IJPSR (2012), Vol. 3, Issue 10 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 02 July, 2012; received in revised form 01 August, 2012; accepted 16 September, 2012

DIABETIC CARDIOMYOPATHY: INSIGHTS INTO PATHOGENESIS, DIAGNOSTIC CHALLENGES, AND THERAPEUTIC OPTIONS

Chintan N. Mehta

Department of Pharmaceutical Sciences, Saurashtra University Campus, University Road, Rajkot-360005, Gujarat, India

Keywords:
Diabetes Mellitus,
Diastolic dysfunction,
Heart Failure,
Pathophysiology,
Treatment

Correspondence to Author:

Chintan N. Mehta

Department of Pharmaceutical Sciences, Saurashtra University Campus, University Road, Rajkot-360005, Gujarat, India

E-mail: chintan_mehta16@rediffmail.com

ABSTRACT

Diabetic cardiomyopathy is the presence of myocardial dysfunction in the absence of coronary artery disease and hypertension. Hyperglycemia seems to be central to the pathogenesis of diabetic cardiomyopathy and to trigger a series of maladaptive stimuli that result in myocardial fibrosis and collagen deposition. These processes are thought to be responsible for altered myocardial relaxation characteristics and manifest as diastolic dysfunction on imaging. Sophisticated imaging technologies also have permitted the detection of subtle systolic dysfunction in the diabetic myocardium. In the early stages, these changes appear reversible with tight metabolic control, but as the pathologic processes become organized, the changes are irreversible and contribute to an excess risk of heart failure among diabetic patients independently of common comorbidities, such as coronary artery disease and hypertension. Therapeutic agents specifically targeting processes that lead to these pathophysiologic changes are in the early stages of development. Although glycemic control and early administration of neuro-hormonal antagonists remain the cornerstones of therapeutic approaches, newer treatment targets are currently being explored.

INTRODUCTION: Diabetic cardiomyopathy was first reported in 1972 by Rubler et al, [1]Who reported the autopsy data from 4 patients with diabetic renal microangiopathy and dilated left ventricles in the absence of other common causes. Diabetic cardiomyopathy as a clinical entity remains elusive, despite more than 3.5 decades of basic and clinical investigations.[2] This is in part because of the lack of consensus over its definition and the underrecognized myocardial abnormalities that are often overlooked. This review aims to examine our current understanding of the importance of diabetic cardiomyopathy as a clinical entity, as it relates to its clinical significance, and the contemporary diagnostic approaches and management options.

Diabetes accounted for a significant percentage of patients with a diagnosis of heart failure in numerous epidemiologic studies [3], The Framingham Study [4], United Kingdom Prospective Diabetes Study [5], Cardiovascular Health Study [6], Euro Heart Failure Surveys [7] all suggested that the presence of diabetes may independently increase the risk of developing incident heart failure.

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Furthermore, worsening glycemic control can compound this risk, and the concomitant diagnoses of diabetes and heart failure may portend a poor prognosis [8]. Clearly, the clinical spectrum of diabetes and heart failure is wide, spanning from overt symptoms to subclinical disease.

However, there are major gaps in our current understanding as to how heart failure develops, especially in the subgroup of patients without an underlying ischemic cause. This is in part because of the lack of comprehensive (and longitudinal) imaging surveys in diabetic patients intended to carefully examine the presence of abnormalities in myocardial structure and performance.

It is in this context that diabetic cardiomyopathy can be clinically defined by the presence of abnormal myocardial performance or structure in the absence of epicardial coronary artery disease, hypertension, and significant valvular disease. This approach was used in its initial description using crude clinical assessment of signs and symptoms in the presence of an increase in cardiothoracic ratios measured by chest x-rays. As illustrated in **(Table-1)** [9-16], several epidemiologic studies have suggested that there is a consistent association between diabetic cardiomyopathy and the presence of cardiac hypertrophy and myocardial stiffness, both independent of hypertension.

Such associations have provided credible evidence to support the existence of diabetic cardiomyopathy as a unique clinical entity, even though the exact pace and the transition of abnormalities in myocardial structure and performance as diabetic cardiomyopathy develops remain to be determined. Although it is not a prerequisite for a patient with diabetes to have preexisting diabetic cardiomyopathy to develop heart failure, the presence of diabetic cardiomyopathy likely portends greater risks of developing heart failure.

TABLE 1: MAIN ECHOCARDIOGRAPHIC, POPULATION-BASED STUDIES ON DIABETIC CARDIOMYOPATHY

Authors	Year	Findings	Population Sample (n)
Galderisi *et al* [9] Framingham Heart Study	1991	Increase of LVM in women	111 DM 381 IGT
Lee *et al* [10] Cardiovascular Health Study	1997	Increase of LVM in both genders	2697 DM or IGT>65 y
Devereux *et al* [11] Strong Heart Study	2000	Increase of LVM, reduction of EFS and MFS	1810 DM
Palmieri *et al* [12] HyperGEN Study	2001	Increase of LVM and RWT, reduction of MFS	386 DM+HTN
Ilercil *et al* [13] Strong Heart Study	2001	Increase of LVM and RWT	457 IGT
Bella *et al* [14] Strong Heart Study	2001	Progressive increase of LVM and reduction of EFS and MFS in DM and DM_HTN	642 DM 874 DM+HTN
Liu *et al* [15] Strong Heart Study	2001	Progressive reduction of E/A ratio and prolongation of DT in DM and DM_HTN	616 DM 671 DM+HTN
Rutter *et al* [16] Framingham Heart Study	2003	Progressive increase of LVM, RWT, and LA in IGT and DM	186 DM 343 IGT

DM = DIABETES MELLITUS; EFS = ENDOCARDIAL FRACTIONAL SHORTENING; HTN = HYPERTENSION; IGT = IMPAIRED GLUCOSE TOLERANCE; LA = LEFT ATRIUM; LVM = LEFT VENTRICULAR MASS; MFS = MID WALL FRACTIONAL SHORTENING; RWT = RELATIVE WALL THICKNESS.

Pathophysiologic Mechanisms of Diabetic Cardiomyopathy: A clear understanding of the precise pathophysiologic mechanisms of diabetic cardiomyopathy is still lacking. However, several pathophysiologic mechanisms have been proposed to explain the structural and functional changes associated with diabetic cardiomyopathy **Figure 1**. These processes are not mutually exclusive and likely act synergistically to develop diabetic cardiomyopathy.

Hyperglycemia is considered to be a central driver in the pathophysiology of diabetic cardiomyopathy because it can trigger several adaptive and maladaptive responses that are evident in diabetic cardiomyopathy. We describe several known mechanisms that have been demonstrated in experimental models.

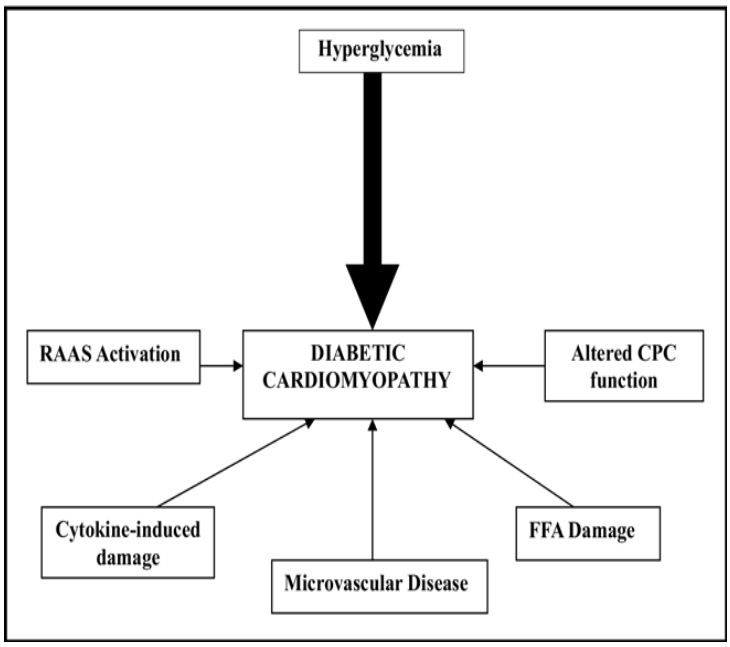

FIGURE 1: **OVERALL SCHEME FOR THE PATHOGENESIS OF DIABETIC CARDIOMYOPATH.** FFA = FREE FATTY ACID; CPC = CARDIAC PROGENETIC CELL; RAAS = RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM.

Free Fatty Acid Metabolism Disturbances: Figure 2 summarizes the role of altered free fatty acid metabolism and its contribution to the development of diabetic cardiomyopathy. **Figure 3** illustrates the role of hyperglycemia in inducing the ultimate downstream effects. In the absence of diabetes, approximately equivalent proportions of energy required for cardiac contractility come from glucose metabolism and free fatty acids; whereas in diabetes, myocardial glucose use is significantly reduced, with a shift in energy production from beta-oxidation of free fatty acids.[17]

This reduction in glucose use in the diabetic myocardium results from depleted glucose transporter proteins, glucose transporter-1 and 4. In addition, free fatty acids inhibit pyruvate dehydrogenase, which impairs myocardial energy production and leads to the accumulation of glycolytic intermediates and ceramide, enhancing apoptosis [18-19], In addition to the effects of free fatty acids on glucose metabolism and oxidative phosphorylation, free fatty acid metabolism for adenosine triphosphate production requires large amounts of oxygen. The toxic intermediates resulting from free fatty acid metabolism[17,20] (so-called lipotoxicity) can impair myocyte calcium handling, worsening myocardial mechanics [21-23].

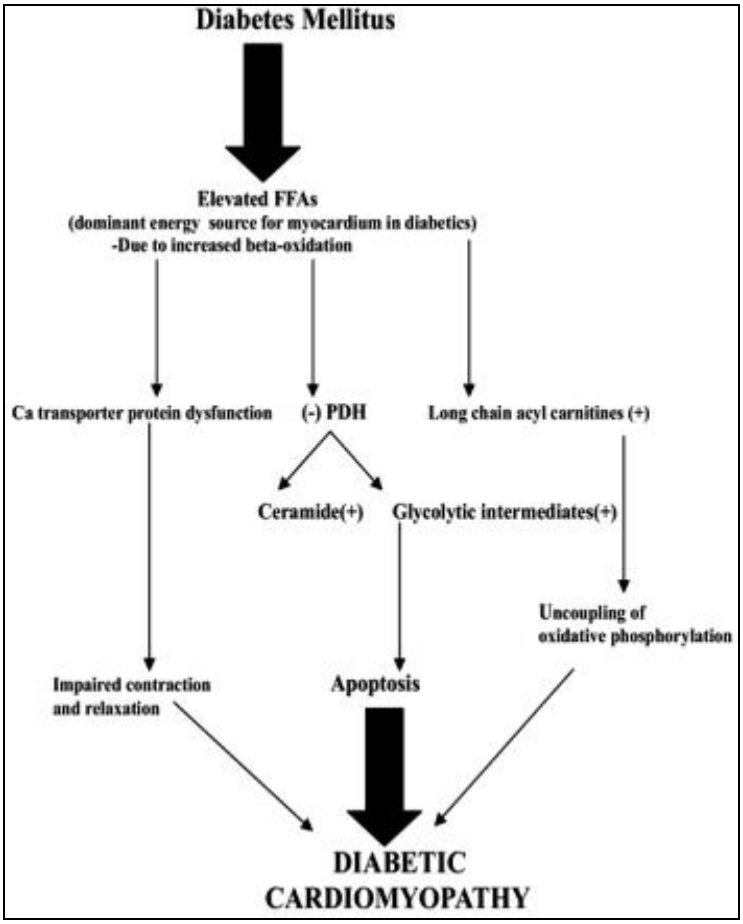

FIGURE 2: THE ROLE OF ALTERED MYOCARDIAL METABOLISM IN THE DEVELOPMENT OF DIABETIC CARDIOMYOPATHY. FFA = FREE FATTY ACID; PDH = PYRUVATE DEHYDROGENASE

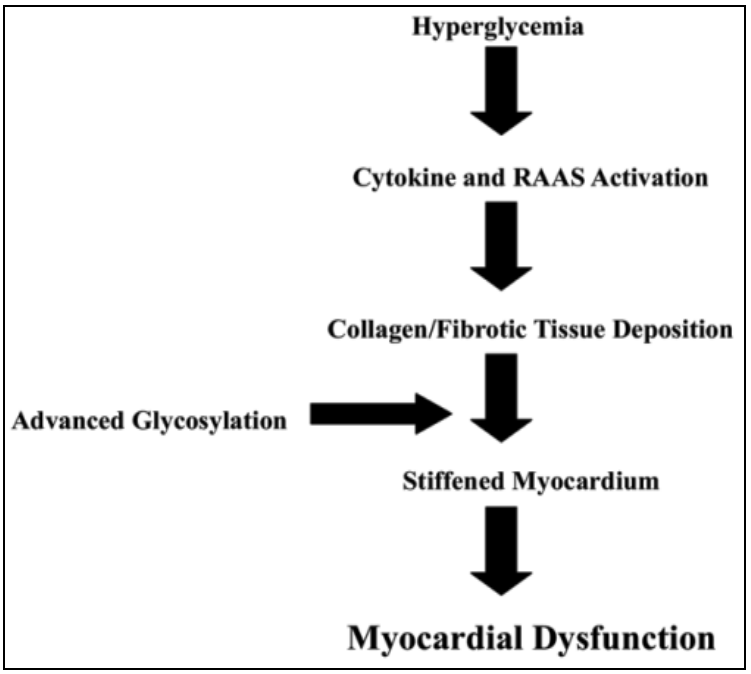

FIGURE 3: EFFECTS OF HYPERGLYCEMIA ON THE DIABETIC MYOCARDIUM. RAAS = RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Clinical Significance:

- Diabetic cardiomyopathy has been a poorly understood entity.
- New research has provided insights into the pathogenesis of diabetic cardiomyopathy, especially the role of hyperglycemia.
- Diabetic cardiomyopathy is defined by echocardiography with myocardial structural or functional abnormalities in the absence of hypertension and coronary disease.
- Diabetic cardiomyopathy might contribute to the excess incidence of heart failure in diabetic patients.
- Treatments specific to diabetic cardiomyopathy are in their early stages of development.

Increased Apoptosis: The diabetic myocardium is susceptible to higher than normal rates of myocyte death by both apoptosis and necrosis. Studies suggest that hyperglycemia results in production of reactive oxygen species, contributing to accelerated apoptosis. Some of this proapoptotic effect of hyperglycemia is triggered by glycosylation and phosphorylation of p53, and excessive synthesis of angiotensin II [24], However, whether increased apoptosis itself is a cause or effect of diabetic cardiomyopathy remains to be determined.

Increased Myocardial Necrosis and Fibrosis: Myocardial fibrosis and collagen deposition are the primary structural changes observed in diabetic cardiomyopathy. Diabetes activates locally active myocardial renin-angiotensin and endothelin systems, contributing to myocyte necrosis and fibrosis [25, 26]. The distribution of fibrous tissue in the myocardium is interstitial, perivascular, or both, and pathologic examination reveals myocardial hypertrophy, interstitial fibrosis, capillary endothelial changes, and capillary basal laminae thickening [27]. Deposition of collagen type I and III predominates in the epicardial and perivascular regions, whereas type IV predominates in the endocardium [28]. Collagen interacts with glucose, forming Schiff bases, which reorganize over the following weeks into glycated collagen (also called Amadori products).

The Amadori products then undergo further chemical modification to form advance glycation end products. The advance glycation end products are a stable form of crosslinked collagen and are thought to contribute to arterial and myocardial stiffness, endothelial dysfunction, and atherosclerotic plaque formation. Correlations between advance glycation end product serum levels and isovolumetric relaxation

time and left ventricular (LV) diameter during diastole have been reported [29]. In the cardiovascular system, advance glycation end products also might perform cross-linking of collagen and circulating proteins (eg, low-density lipoprotein), and result in impaired cellular nitric oxide signaling through advance glycation end product receptor interactions. Advance glycation end products also exacerbate intracellular oxidative stress, which can contribute to cell damage [31]. Therefore, altered myocardial reflectivity and impaired LV function (both diastolic and systolic) observed in patients with diabetes can be the result of fibrosis and altered collagen structure, specifically because of increased collagen cross-linking or formations of advance glycation end products [31, 32].

Diabetes also is characterized by low insulin-like growth factor-1 and elevated transforming growth factor-β_1 levels. Resistance to insulin-like growth factor-1, characteristic of diabetes, results in myocyte necrosis, LV hypertrophy (LVH), and myocardial dysfunction [33]. Hyperglycemia and hyperinsulinemia stimulate overexpression of transforming growth factor- β_1 by cardiac fibroblasts, resulting in fibrous tissue deposition and extracellular matrix synthesis [34], which also might contribute to myocardial dysfunction.

Disordered Copper Metabolism: Recently, alterations in copper metabolism have been proposed as an important contributor to the progression of diabetes-related cardiovascular complications, including diabetic cardiomyopathy. Elevated serum copper levels are found in patients with diabetes, and the highest levels are found in those with microvascular complications and hypertension [35]. Hyperglycemia can damage the copper binding properties of ceruloplasmin and albumin (the main copper binding proteins in plasma), resulting in increased copper levels in the extracellular matrix [36, 37].

Glycated proteins also might have an increased affinity toward copper [38, 39] Therefore, an abundance of copper in the extracellular matrix is thought to activate the oxidation–reduction system, leading to an enhanced production of free radicals resulting in increased oxidative stress and fibrosis [40].

Autonomic Neuropathy: Diabetic autonomic neuropathy can lead to changes in sympathetic innervations and subsequent disordered adrenergic receptor expression and altered catecholamine levels in the myocardium. An increased expression of the β_1-receptor results in enhanced apoptosis, fibrosis, hypertrophy, and impaired myocardial function [41].

Stem Cell Involvement: Evidence from a new study suggests that diabetic cardiomyopathy may be a stem cell disease. In this study, enhanced oxidative stress in diabetes can alter cardiac progenitor cell function, leading to defective cardiac progenitor cell growth and myocyte formation, causing premature myocardial aging and heart failure. In addition, the authors noted that cardiac progenitor cell apoptosis and heart failure were ameliorated by ablation of the p66shc gene, possibly responsible for promoting the senescent phenotype [42].

Microvascular Disease and Endothelial Dysfunction: Diabetes is recognized by characteristic changes in microvascular architecture. These changes include abnormal capillary permeability, microaneurysm formation, subendothelial matrix deposition, and fibrosis surrounding arterioles. Coronary blood flow reserve in diabetic patients is reduced even in the absence of obstructive coronary artery disease and LVH [43]. Hyperglycemia also can lead to an enhanced synthesis of vasoconstrictor prostanoids by the endothelium and activation of protein kinase C. This vasoconstriction can promote myocardial hypertrophy, endothelial dysfunction, and ventricular hypertrophy [44, 45].

Protein kinase C, an intracellular signaling molecule, is activated in diabetes and can lead to endothelial dysfunction by reducing the bioavailability of nitric oxide while increasing oxygen-derived free radical production. It also can enhance leukocyte adhesion, increase albumin permeability, and impair fibrinolysis [46, 47]. Therefore, activation of this enzyme contributes significantly to the development of microvascular complications, as seen in diabetic neuropathy and nephropathy.

Diagnosing Diabetic Cardiomyopathy: There are 2 important components in the clinical diagnosis of diabetic cardiomyopathy: the detection of myocardial abnormalities and the exclusion of other contributory causes of cardiomyopathy. An important challenge in the clinical diagnosis of diabetic cardiomyopathy has been the lack of any pathognomonic histologic changes or imaging characteristics associated with the diagnosis. Endomyocardial biopsies are not indicated because of their invasiveness, unless circumstances to suspect other causes of cardiomyopathy in the differential diagnosis exist (eg, hypertrophic cardiomyopathy and infiltrative heart diseases). Nevertheless, the presence of myocardial fibrosis or collagen deposition can be fairly characteristic of diabetic cardiomyopathy. Electron microscopic features, including mitochondrial abnormalities, fatty acid deposits, or even myocyte hypertrophy, can be evident.

The diagnosis of diabetic cardiomyopathy currently rests on noninvasive imaging techniques that can demonstrate myocardial dysfunction across the spectra of clinical presentation. In patients with overt heart failure, the presence of echocardiographic features of cardiac dysfunction or structural abnormalities is often confirmatory. However, in the absence of overt symptoms (so-called Stage B heart failure in the American College of Cardiology/American Heart Association Staging of chronic heart failure), an imaging diagnosis is warranted.

Table 2 lists selective echocardiographic studies in diabetic cardiomyopathy. It is important to emphasize that with our current knowledge, there is still no consensus in the precise imaging definition of diabetic cardiomyopathy, but evidence of hypertrophy or diastolic dysfunction is likely crucial to support a diagnosis of diabetic cardiomyopathy, but is not specific to it. On the basis of our review of the literature, we propose an imaging definition of diabetic cardiomyopathy that includes either orboth features listed as follows:

a) Evidence of cardiac hypertrophy determined by conventional echocardiography or cardiac magnetic resonance imaging;

b) Evidence of LV diastolic dysfunction (with or without LV systolic dysfunction), either clinically by transmitral Doppler or tissue Doppler imaging (TDI), or evidence of left atrial enlargement; or subclinically by novel imaging techniques or provocative testing (eg, strain and strainrate imaging or stress imaging).

TABLE 2: SELECTED ECHOCARDIOGRAPHIC STUDIES ON DIABETIC CARDIOMYOPATHY

Author(s)	Year	Population Sample (n)	Findings
Zabalgoitia *et al* [50]	2001	86 normotensive men and women (mean age 46 ± 6 y)	Diastolic dysfunction by E/A ratio reversal in 30% of subjectsv in the absence of HTN and microvascular disease. Additional 17% diagnosed with "pseudonormalized" pattern using Valsalva maneuver.
Poirier *et al* [51]	2001	46 men with DM aged 38-67 y	Diastolic dysfunction by E/A ratio reversal in 32%. Additional 28% diagnosed with "pseudonormalized" pattern using Valsalva maneuver.
Boyer *et al* [64]	2004	61 consecutive normotensive patients with DM	Diastolic dysfunction found in 43/57 patients (75%) using various echocardiographic techniques. TDI detected diastolic dysfunction more often (63%) than any other echocardiographic approach.
Di Bonito *et al* [65]	2005	40 non-obese, normotensive, uncomplicated DM subjects 20 control subjects	With TDI, diabetic subjects had a lower Ea/Aa ratio (*P* <.0001) compared with controls. Linear regression analysis showed that insulin resistance by HOMA-IR was negatively associated with Ea/Aa ratio (*P*=.026).
Fang *et al* [66]	2003	48 with DM only 45 with LVH only 45 with both DM and LVH 48 normal controls	All patient groups showed reduced systolic function compared with controls, evidenced by lower peak strain (*P* < .001) and strain rate (*P*=.005). Calibrated integrated backscatter, signifying myocardial reflectivity, was greater in each patient group than in controls (*P* < .05).
Fang *et al* [67]	2005	219 unselected patients with DM without known cardiac disease underwent resting and stress echocardiography. After exclusion of CAD or LVH, the remaining 120 patients studied with TDI.	Significant subclinical LV systolic dysfunction present in 27% of diabetic subjects. Myocardial systolic dysfunction by peak strain independently associated with HBA1C level (*P* <.001) and lack of ACE inhibitor (*P*=.003).
Von Bibra *et al* [68]	2005	43 asymptomatic diabetic subjects and 33 nondiabetic controls, with normal LV function and no clinical signs of HF Investigated with TDI at rest and pharmacologic stress with dipyridamole and/or dobutamine	Diastolic and systolic myocardial dysfunction in patients with DM was identified by quantitative TDI before the onset of clinical signs of HF and before the appearance of traditional echocardiographic indices of systolic myocardial dysfunction.
Ha *et al* [69]	2007	53 subjects with DM 53 subjects with age and gender-matched control. None with echocardiographic evidence of myocardial ischemia	No significant differences in mitral inflow velocities at rest. Changes of systolic and diastolic velocities of the mitral annulus during exercise were significantly reduced in patients with DM. TDI with exercise appeared helpful in identifying early myocardial dysfunction in patients with DM.

Von Bibra *et al* [61]	2004	A total of 25 patients with DM were subjected to intensified metabolic control based on an increased dose of insulin (group A: n=16), or oral treatment (group B: n=9). Eight patients were studied as controls with no changes in medication regimen.	Despite favorable effects on body composition, metabolism, and exercise capacity, the 1-y lifestyle intervention engendered no effect on myocardial function in diabetic patients. However, diabetic patients with poor baseline myocardial function, body composition, glycemic control, and cardiorespiratory fitness showed greater improvements in myocardial function.
Von Bibra *et al* [62]	2007	Metabolic control and myocardial function evaluated in 88 patients (33 short term [25 with intensive control and 8 controls] and 50 long term [33 with intensive control and 17 controls]) with DM. Systolic (Vs) and diastolic (Ve) myocardial velocity assessed by TDI.	In the long-term study group, fasting serum glucose was reduced by 20±43 mg/dL ($P < .017$) compared with baseline and was associated with a significant increase in myocardial velocity. Serum glucose and myocardial velocities remained unchanged in the control group.
Hordern *et al* [63]	2007	223 diabetic patients: 112 patients assigned to usual care and 111 patients assigned to exercise training and dietary advice for 1 y	Despite favorable effects on body composition, metabolism, and exercise capacity, the 1-y lifestyle intervention engendered no effect on myocardial function in diabetic patients. However, diabetic patients with poor baseline myocardial function, body composition, glycemic control, and cardiorespiratory fitness showed greater improvements in myocardial function.

ACE = ANGIOTENSIN-CONVERTING ENZYME; DM = DIABETES MELLITUS; HTN = HYPERTENSION; TDI = TISSUE DOPPLER IMAGING; LVH = LEFT VENTRICULAR HYPERTROPHY; CAD = CORONARY ARTERY DISEASE; LV = LEFT VENTRICULAR; HF = HEART FAILURE; HOMA-IR = HOMEOSTATIS MODEL ASSESMENT-INSULINE RESISTANCE; HBA1C = GLYCOSYLATED HEAMOGLOBIN.

Evidence of Cardiac Hypertrophy: Cardiac hypertrophy is readily demonstrable by conventional echocardiographic techniques and is a hallmark in the morphologic manifestation of diabetic cardiomyopathy, generally representing a more advanced stage of disease. The presence of hypertrophy in diabetic cardiomyopathy might not be associated with demonstrable LV diastolic dysfunction by conventional echocardiography (and vice versa). The availability of cardiac magnetic resonance imaging has broadened our understanding of diabetic cardiomyopathy, with the demonstration of fatty or fibrosis infiltrates in the hypertrophied myocardium,as well as a noticeable alteration in the myocardial geometry and increases in ventricular mass.

Human cardiac magnetic resonance imaging studies assessing diabetic cardiomyopathy are in their infancy compared with echocardiography, but have demonstrated increased cardiac torsion. This unexpected finding has been thought to represent a propensity to future cardiac dysfunction in asymptomatic diabetic subjects [48, 49].

Regression of LVH has been demonstrated with some interventions targeting diabetic cardiomyopathy. However, unlike hypertensive cardiomyopathy, the clinical significance of hypertrophy and its regression in diabetic cardiomyopathy remain to be determined.

Evidence of Left Ventricular Diastolic: Diastolic dysfunction has received much focus in crosssectional clinical studies that explored the association between a wide range of Doppler-derived variables.[50,51] Early studies demonstrated that abnormalities in transmitral Doppler inflow patterns were associated with poor glycemic control and presence of cardiac structure abnormalities [52-60]. Also, improvement in glycemic control has demonstrated the return to a more normal profile, suggesting that the process might be reversible in its early stages [61-63]. The availability of newer modalities has paved the way to more consistent measurements of diastolic dysfunction.

TDI uses the ability of detecting changes in the movements of the mitral valve by Doppler imaging signals at specified myocardial locations adjacent to the mitral annulus.

By using a combination of transmitral Doppler (E) and TDI indices (E =), the ratio of mitral E/E = has been used to detect the presence of impaired LV compliance (and to some extent an estimate of LV end-diastolic pressure). In several surveys of diabetic patients without overt signs and symptoms of heart failure, TDI studies have helped uncover subtle abnormalities and have identified diastolic dysfunction in a significantly higher number of asymptomatic subjects than conventional Doppler echocardiography [64, 65].

These studies have shown that diabetic patients without coronary artery disease have impaired systolic function, increased myocardial reflectivity, and myocardial hypertrophy, similar to hypertension.[66] An independent association between myocardial systolic dysfunction with increasing glycosylated hemoglobin levels also has been observed in TDI studies [67]. One important but often overlooked structural indicator of diastolic dysfunction is the presence of left atrial enlargement, often present in patients with diastolic dysfunction. However, studies have not specifically evaluated the value of this parameter in diabetic cardiomyopathy. It is important to emphasize that other factors also can contribute diastolic dysfunction.

For example, microvascular myocardial ischemia may lead to significant diastolic dysfunction and diastolic heart failure.

Subclinical Left Ventricular Dysfunction: Our ability to detect subtle changes in signals from advanced imaging techniques, such as speckle-tracking or strain imaging, has provided even greater insights into early manifestations of myocardial dysfunction that may be "precursors" of the development of diabetic cardiomyopathy and may lead to earlier detection. Another approach involves the use of stress modalities to "unmask" the presence of underlying diabetic cardiomyopathy.

The adverse effect of diabetes on myocardial function, not evident at rest imaging, can be uncovered by stress TDI [68,69]. Because stressinduced myocardial dysfunction is the earliest detectable manifestation of diabetic cardiomyopathy, the effect of strict glycemic control on reversal of early myocardial dysfunction also has been evaluated. An improvement in metabolic control has been shown to enhance myocardial contractility parameters, which has been explained with more efficient myocardial energy substrate use and improved microvascular perfusion.[61-63]. **Figure 4** shows an echocardiographic image of a patient with diabetic cardiomyopathy with LVH.

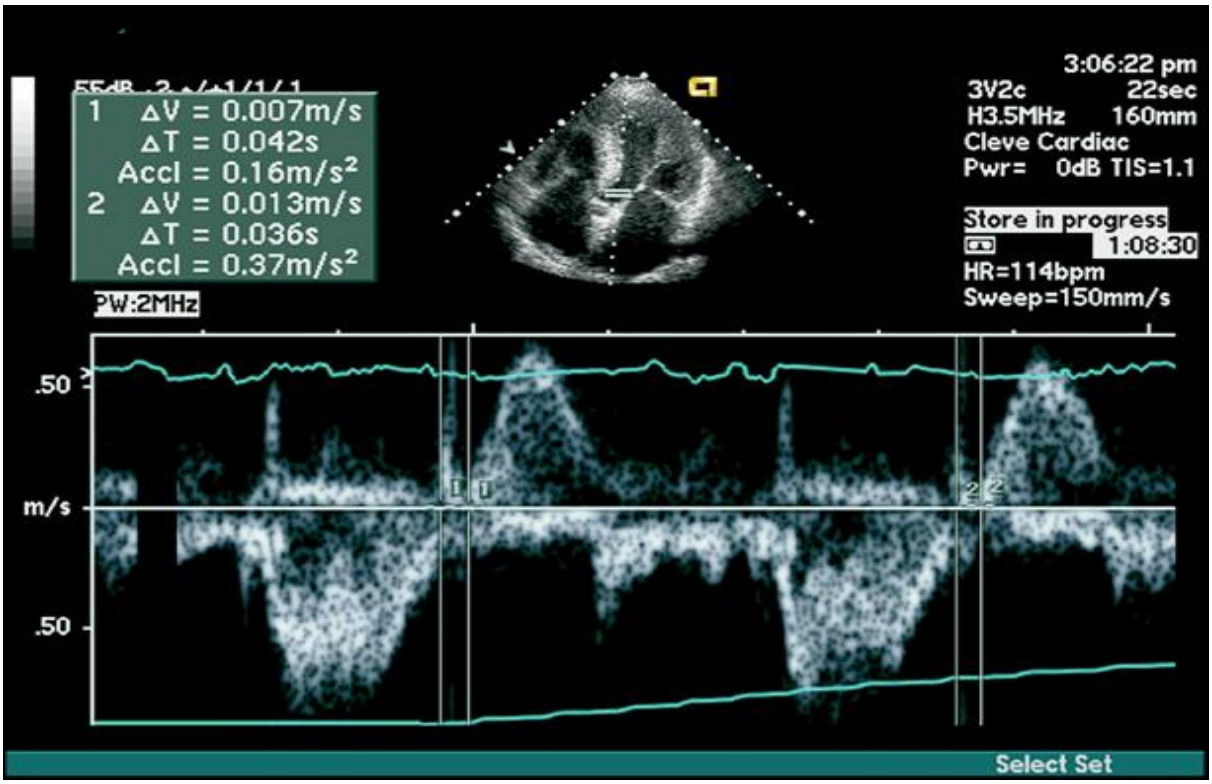

FIGURE 4 : ECHOCARDIOGRAPHIC IMAGE OF A PATIENT WITH DIABETIC CARDIOMYOPATHY WITH VENTRICULAR HYPERTROPHY

Prevention and Therapy:

1. **Glycemic Control:** The prevention and treatment of diabetic cardiomyopathy are clinically relevant because of its role in the pathogenesis of heart failure. Although the effect of glycemic control on diabetic cardiomyopathy has been studied in only a limited fashion, evidence suggests that good glycemic control is beneficial, at least in the early stages of myocardial dysfunction.[61-63] Evidence also suggests that diabetic cardiomyopathy does not develop in patients with tightly controlled type 1 diabetes, supporting an important role for hyperglycemia in the pathogenesis of diabetic cardiomyopathy.[70] Hyperglycemia is responsible for microvascular complications in diabetes, and because microvascular alterations are thought to contribute significantly to the pathogenesis of diabetic cardiomyopathy, good glycemic control is perhaps the most important component in the overall management of diabetic cardiomyopathy.

Firm recommendations regarding the choice of current glucose-lowering therapies in patients with diabetic cardiomyopathy cannot be made because of a lack of evidence. However, glucagon-like peptide-1 analogues have demonstrated improved hemodynamic variables in diabetic patients without overt heart failure. Improved cardiac parameters also have been noted with this agent class in postinfarction and in populations with advanced heart failure [71].

On the other hand, the use of thiazolidinediones in the management of patients with diabetic cardiomyopathy is problematic because of a propensity for fluid overload. In general, the choice of antidiabetic therapy in diabetic cardiomyopathy should be dictated by clinical characteristics, such as the presence or absence renal dysfunction, risk of hypoglycemia, age, volume status, and concomitant drug therapy.

Neurohormonal Antagonism: The important role of the renin-angiotensin-aldosterone system in the pathogenesis of complications in diabetic patients is well described. Evidence supports the use of angiotensin-converting enzyme inhibitors in preventing myocardial fibrosis, cardiac hypertrophy, and myocardial mechanical dysfunction associated with diabetic cardiomyopathy [72-74].

Angiotensin-converting enzyme inhibition and angiotensin-1 receptor blockade also have been shown to prevent coronary perivascular fibrosis and collagen deposition [75]. The angiotensin receptor blocker, candesartan, can improve echocardiographic parameters of diastolic dysfunction, reduce collagen synthesis, and increase collagen degradation in asymptomatic diabetic subjects [76]. Evidence also suggests a beneficial effect of aldosterone antagonism in diastolic heart failure by virtue of their beneficial effects on cardiac hypertrophy and fibrosis [77, 78]. These findings underscore the critical importance of inhibiting the renin-angiotensin-aldosterone system in diabetic patients, especially when diastolic dysfunction is present and the process is partially reversible.

Novel Therapies Targeting Diabetic Cardiomyopathy: Therapies directed toward the prevention and progression of diabetic cardiomyopathy are in the early stages of clinical development and have targeted either enhanced fibrosis/ collagen deposition or alterations in cardiomyocyte metabolism. The majority of the agents listed below are in experimental stages, and none of them have been approved for use in diabetic cardiomyopathy. Notable among these novel agents are advance glycation end product inhibitors (eg, aminoguanidine, alanine aminotransferase 946, and pyridoxamine); advance glycation end product cross-link breakers (eg, alanine aminotransferase 711); and copper chelation therapy (eg, trientine).

Modulators of free fatty acid metabolism, such as trimetazidine, have proven useful in the management of angina, but their efficacy on diabetic cardiomyopathy is unknown. Exenatide (recombinant glucagon-like peptide-1, a Food and Drug Administration-approved glucose-lowering agent) has yet to be studied specifically in patients with diabetic cardiomyopathy patients despite promising cardiac effects with glucagon-like peptide-1 infusion in mechanistic studies.

CONCLUSIONS Diabetic cardiomyopathy has progressed from a nebulous concept to concrete reality during the last 3 decades. Multiple pathophysiologic mechanisms have been proposed to explain this entity, but hyperglycemia seems to be the central mechanism triggering the processes that lead to the ultimate pathologic changes of myocardial hypertrophy, fibrosis,

and collagen deposition. From epidemiologic studies, the natural history of diabetic cardiomyopathy seems to start with impaired glucose tolerance and possibly takes years to reach overt LV systolic or diastolic dysfunction. The development of therapeutic agents designed toward the specific metabolic and structural derangements of diabetic cardiomyopathy is encouraging and deserves further evaluation.

It should be clarified that heart failure in diabetic patients is not an advanced stage of diabetic cardiomyopathy but results from a constellation of pathophysiologic processes, an important one of which is diabetic cardiomyopathy. Therefore, diabetes-specific therapeutic measures are likely to succeed at earlier stages of myocardial dysfunction, underscoring the efforts to develop strategies for early detection, especially with conventional and novel imaging techniques.

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How to cite this article:
Chintan N. Mehta: Diabetic Cardiomyopathy: Insights into Pathogenesis, Diagnostic Challenges, and Therapeutic Options. *Int J Pharm Sci Res*. 3(10); 3565-3576.