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An Overview about diabetic cardiomyopathy associated type 2 diabetes

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Abstract: The risk for development of cardiac stiffness/diastolic dysfunction is also high in those with type 2 diabetes. For example, observations from the Framingham Heart Study indicated that persons with type 2 diabetes had a two- to eight fold increased risk for development of heart failure and that 19% developed symptoms of heart failure. The pathophysiological processes behind DCM remain incompletely understood. There are several hypothesized mechanisms for the multifactorial occurrence of DCM, such as insulin resistance, microvascular impairment, abnormalities in subcellular components, metabolic disturbances, cardiac autonomic dysfunction, changes in the renin-angiotensin-aldosterone system (RAAS), and maladaptive immune response. The majority 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)..

Keywords: diabetic cardiomyopathy, type 2 diabetes

Introduction: Diabetic cardiomyopathy is a specific form of heart disease, which occurs independent of other cardiac risk factors such as coronary artery disease (CAD) and hypertension, promoted by resistance to the metabolic actions of insulin in heart tissue (e.g. insulin resistance), compensatory hyperinsulinaemia and the progression of hyperglycaemia**(1).**

The diagnosis of diabetic cardiomyopathy as a separate condition was made in 1972 after indications of heart failure were observed in four diabetic patients. This was supported by a 1974 secondary analysis of the Framingham Heart Study, which discovered that, after controlling for other risk factors such as age, hypertension, obesity, dyslipidemia, and CAD, the risk of heart failure was elevated in men and women with diabetes by 2.4 and 5 times, respectively, compared to those without the disease **(2)**.

A 1977 study of 17 people with type 2 diabetes used angiography to rule out coronary artery disease (CAD). This allowed for the definitive identification of diabetic cardiomyopathy, which is characterized by elevated cardiac left ventricular end-diastolic pressure, decreased left ventricular compliance, and low left ventricular ejection fraction with diffuse hyperkinesia. These first findings revealed that diabetes was directly and specifically related to interstitial fibrosis, which in turn was linked to decreased left ventricular compliance and diastolic dysfunction **(2)**.

The prevalence of diabetic cardiomyopathy associated type 2 diabetes

The risk for development of cardiac stiffness/diastolic dysfunction is also high in those with type 2 diabetes. For example, observations from the Framingham Heart Study indicated that persons with type 2 diabetes had a two- to eight fold increased risk for development of heart failure and that 19% developed symptoms of heart failure **(2)**.

A retrospective cohort study of 8,231 individuals with type 2 diabetes indicated that heart failure developed in 30.9 out of 1000 persons, compared with an incidence of 12.4 per 1000 in individuals without diabetes, indicating a 2.5-fold increase in heart failure risk in those with type 2 diabetes. Furthermore, an observational study involving 25,958 men and 22,900 women with type 2 diabetes indicated that a 1% increase in of HbA1c was associated with an 8% increase in the risk of heart failure, independent of blood pressure, obesity, age and the presence of CAD, suggesting that type 2 diabetes is an independent risk for incident heart failure **(2)**.

Conversely, in a prospective observational study, each 1% reduction in HbA1c level was associated with a 16% reduction in risk for heart failure, 14% reduction in risk for myocardial infarction and 21% reduction in risk for deaths related to type 2 diabetes . These data support the notion that glycaemic control in those with type 2 diabetes is a critical mechanism in the prevention of cardiac dysfunction and heart failure**(2)**.

Pathophysiological mechanisms of diabetic cardiomyopathy

The pathophysiological processes behind DCM remain incompletely understood. There are several hypothesized mechanisms for the multifactorial occurrence of DCM, such as insulin resistance, microvascular impairment, abnormalities in subcellular components, metabolic disturbances, cardiac autonomic dysfunction, changes in the renin-angiotensin-aldosterone system (RAAS), and maladaptive immune response

A long-standing theory states that while numerous intricate processes and the interaction of numerous metabolic and molecular events within the heart and plasma contribute to its pathophysiology, hyperglycemia plays a crucial role in the development of DCM.

The main metabolic abnormalities associated with diabetes mellitus are hyperglycemia, inflammation, and hyperlipidemia. These conditions all lead to the generation of reactive oxygen species (ROS), or nitrogen species, which are responsible for the majority of diabetic complications, such as DCM and diabetic nephropathy **(3) .**
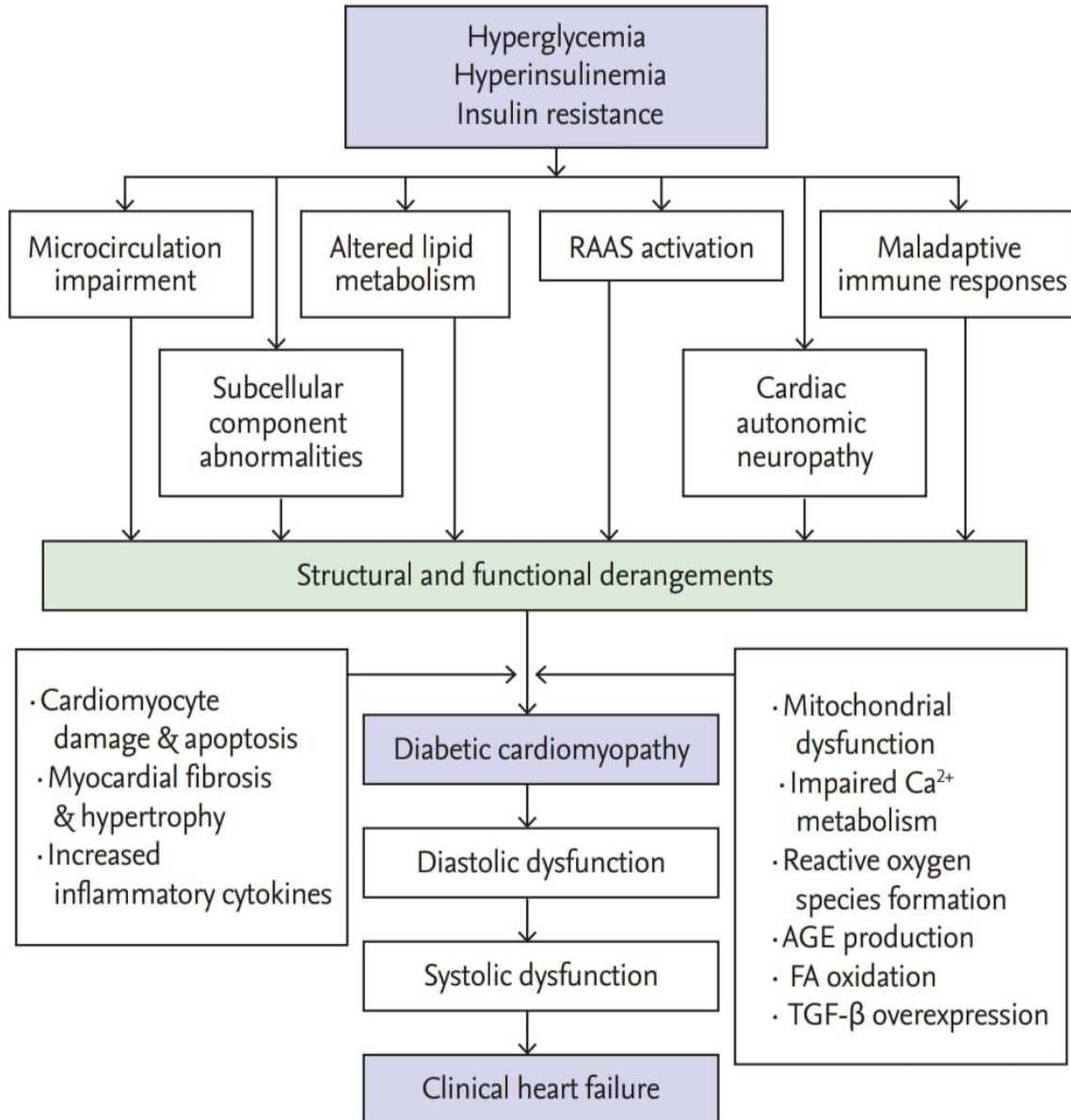

Figure 1 . Pathophysiological mechanisms of diabetic cardiomyopathy **(4).**

RAAS, renin-angiotensin-aldosterone system; AGE, advanced glycation end product; FA, fatty acid; TGF-β, transforming growth factor-β

Effects of hyperglycemia on the heart

Cardiomyocytes undergo several molecular and metabolic alterations as a result of chronic hyperglycemia. Hyperglycemia-induced increased glucose metabolism raises oxidative stress by causing ROS to form in the mitochondria. The overproduction of superoxide in the mitochondrial respiratory chain causes oxidative stress, which in turn reduces cardiac contractility and eventually causes myocardial fibrosis. **(5).**

ROS and oxidative stress can hasten cellular DNA damage and cardiomyocyte apoptosis. Poly ADP ribose polymerase (PARP), one of the DNA repair enzymes, is similarly activated by oxidative stress-induced DNA damage. By diverting the normal glycolytic pathway for glucose metabolism, 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 have a significant role in diabetes complications can be covalently crosslinked by AGEs. Myocardial stiffness and reduced cardiac relaxation are the outcomes of the elastin and collagen crosslinking. AGEs harm the heart in both humans and animals**(6).**

Cardiac autonomic neuropathy in diabetic cardiomyopathy

A previous study reported a relationship between the development of DCM and nervous system activation states **(7).**

Sympathetic nervous system activation raises β1-adrenergic expression and signaling, which promotes Cardiomyocyte hypertrophy, interstitial fibrosis, and reduced contractile performance along with a rise in Cardiomyocyte apoptosis **(8).**

Heart failure is associated with decreased acetylcholinesterase activity, altered muscarinic receptor density and composition, and decreased parasympathetic nervous system activation. Cardiovascular remodeling and clinical outcomes may benefit directly from direct or indirect stimulation of the vagus nerve **(9).**

CAN is a chronic complication of diabetes mellitus that causes irregularities in cardiac rhythm and vascular hemodynamics. In people with a persistent history of diabetic mellitus, the prevalence of various degrees of CAN may reach 60%. CAN changes the myocardium's contractile activity and affects coronary circulation 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 . There have also been reports of correlations between the severity of CAN and the prevalence of diastolic dysfunction . Patients with diabetic CAN exhibit altered myocardial contractility responses in response to stress, and exercise-induced MD has been shown in patients with resting normal ventricular function **(4).**

Contributions of insulin resistance and hyperinsulinemia

In T2DM and prediabetic situations, insulin resistance and hyperinsulinemia are common clinical abnormalities. By a number of pathways, hyperinsulinemia causes Cardiomyocyte hypertrophy. Diabetes mellitus-related Cardiomyocyte hypertrophy is transcriptionally regulated. Hyperinsulinemia induces a number of 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 major 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).**

Cytoplasmic AGT II promotes cell growth in animal models. AGT II directly affects cell signaling, which causes Cardiomyocyte hypertrophy and cardiac fibroblast proliferation. 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. Moreover, via triggering the mammalian target of rapamycin-S6 kinase 1 signal transduction pathway, the increased activation of mineralocorticoid receptor signaling and AGT II may promote insulin resistance **(12).**

Effects of altered lipid metabolism on the myocardium

The heart can use both glucose and fatty acids (FAs) as energy sources under physiological conditions. 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 uptaked **(13).**

In order to supply cardiac energy substrates, nutrients stimulate myocardial insulin signaling and raise plasma insulin levels. This in turn facilitates the translocation of GLUT4 and CD36 to the myocyte sarcolemma**(13)**.

On the other hand, GLUT4 internalizes and returns to its intracellular position in T2DM and/or insulin resistance situations, while CD36 preferentially localizes to the sarcolemma**(14).**

The reciprocal positioning of CD36 and GLUT4 influences the genesis of cardiac metabolic abnormalities that are characterized by metabolic inflexibility. As a result, in diabetes mellitus, the decreased glucose uptake brought on by cardiac and systemic insulin resistance encourages a substrate shift toward greater free fatty acid (FFA) oxidation, which lowers cardiac efficiency **(15).**

The lipotoxicity characterized by the excessive accumulation of FAs in the myocardium reduces normal physiological autophagy and impairs insulin signaling. This results in structural and morphological changes as well as decreased cardiac function. These abnormalities can decrease the efficiency of muscle fiber function in response to electrical stimulation and promote myocardial oxygen consumption **(8).**

In non-adipose tissues such the heart, liver, and skeletal muscle, ectopic lipid accumulation results from Overstrain of the cellular oxidation capacity in diabetes mellitus. It was suggested that cardiac steatosis is a major cause of DCM **(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 is likely to surpass the capability of mitochondrial oxidative enzymes, resulting in lipotoxic damage to the myocardium. A portion of the extra FA enter nonoxidative pathways, where they produce harmful FA intermediates like ceramide. Following their interference with normal cellular signaling, these toxic chemicals cause apoptosis, cellular damage, mitochondrial dysfunction, and ultimately contractile dysfunction and cardiac fibrosis **(17).).**

Increased FA oxidation in the mitochondria is associated with the Increased production of reactive oxygen species (ROS) in the mitochondria is linked to increased oxidation of cytoplasmic lipids to lipid peroxides, which in turn cause damage to the mitochondria and cells as well as the disconnection of mitochondrial oxidative metabolism **(17).**

This results in reduced cardiac contractility and impaired energy production in the myocardium, and impaired mitochondrial calcium handling also causes cardiac dysfunction **(18).**

Lipotoxicity-induced cellular apoptosis is commonly referred to as lipoapoptosis; various mechanisms may induce lipoapoptosis, including palmitate toxicity, ER stress, diacylglycerol and ceramide formation, inflammation, and membrane destabilization .The effects of lipoapoptosis on cardiac function include myocardial fibrosis and structural damage **(17).**

Maladaptive immune responses

Changes in the innate and adaptive immune systems can promote DCM **(19)**.

Insulin resistance or obesity frequently trigger the activation of macrophage polarization to traditional (M1) or alternative (M2) phenotypes and proinflammatory T helper cells **(2)**.

Furthermore, persistent overfeeding triggers immunological reactions in white adipose tissue that lead to low-grade inflammation. In insulin-resistant and obese conditions, macrophage M2 polarization elicits an anti-inflammatory response, while macrophage M1 polarization elicits a pro-inflammatory response**.** M1 macrophages release pro-inflammatory cytokines that impair systemic and cardiac insulin signaling and promote the development of DCM **(2)**.

On the other hand, M2 macrophages release interleukin 10 and macrophage mannose receptor 1, which inhibit the development of Cardiomyocyte hypertrophy and cardiac fibrosis. Patients with DCM were shown to have T helper lymphocytes, another subset of immune cells. A higher CD8+:CD4+ T-cell ratio is found in the visceral adipose tissue of mice fed a high-fat diet compared with lean mic **(20)**.

Insulin resistance brought on by diet also causes a substantial rise in the fraction of type 1 T helper-polarized cells, while type 2 T helper-polarized cells are cut by around half. Based on their post-activation cytokine expression profile, these cells can be subtyped **(20)**.

Cardiac fibrosis and poor diastolic relaxation are exacerbated by T helper cells' enhanced secretion of chemokines, growth factors, and proinflammatory cytokines . Regulatory T-cells, on the other hand, typically reduce the proinflammatory effects of T helper cells in the heart **(21).**

Subcellular component abnormalities

Metabolic abnormalities involving endoplasmic reticulum (ER) stress, impaired calcium handling, and mitochondrial dysfunction are associated with the pathogenesis of DCM **(22).**

The overproduction of ROS damages the ER by impairing post-translational modifications and protein folding in the rough ER. When the ER is under stress, an adaptive response is triggered, which accelerates the proteasomes' breakdown of misfolded proteins. Nutrient overflow into cells under conditions of high fat and carbohydrate intake and insulin resistance results in the transfer of electrons to oxygen without the production of adenosine triphosphate (ATP) and also increases ROS, which may cause oxidative damage within mitochondria. Consequently, components of the lipid membrane, proteins, and DNA are damaged by mitochondrial ROS production, and the accumulation of ROS-mediated fibrosis causes diastolic dysfunction, which can lead to heart failure **(4)**.

DCM and diastolic dysfunction are the results of impaired calcium management brought on by oxidative stress and ER. ROS, long-chain acylcarnitines, and abnormal membrane lipid content in the mitochondrial membrane, such as via cardiolipin, can alter calcium handling by affecting various transporter proteins; thus, inducing delayed diastolic relaxation and impaired intracellular calcium uptake **(8)**.

Autophagy, necrosis, and apoptosis are the final outcomes of subcellular component malfunction that is enhanced by the interplay of aberrant calcium handling, ROS, and ER stress **(22)**.

Microcirculation impairment in the myocardium

The pathological characteristic of diabetes-related vascular complications is damage to the microcirculation throughout the body. Unique examples of microvascular complications inlcude diabetic nephropathy, neuropathy, and retinopathy ,microcirculation impairment in the myocardium **(23)**.

Patients with T2DM, insulin resistance, and DCM often have compromised coronary microvasculature. 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 take place in settings of decreased insulin sensitivity **(23)**.

Diabetes mellitus patients' cardiac circulation is shown to have reduced capillary length density and hyaline-related alterations in the medial arteriolar layers. The medium and small arterioles of the diabetic heart sustain further damage from the decreased blood flow brought on by microcirculatory dysfunction affecting the vasa vasorum in diabetes mellitus. Other vascular diseases that lead to cardiac microvascular ischemia in diabetes mellitus include thickening of the capillary basement membrane, microaneurysm development in tiny arteries, and perivascular fibrosis and interstitial alterations. Ischemia contributes to myocardial fibrosis, stiffness, and dysfunction in DCM. **(4)**.

Both small and large blood vessels might become stiff due to insulin resistance and hyperinsulinemia . One possible explanation for the observed increase in vascular stiffness is that hyperinsulinemia stimulates the development of vascular smooth muscle cells to an osteoblast-like phenotype. By raising osteocalcin expression, alkaline phosphatase activity, and the development of mineralized nodules in vascular smooth muscle cells through elevated levels of receptor activator of nuclear factor κB, elevated insulin levels may also increase vascular stiffness **(24)**.

Therefore, a higher chance of developing CAD in conjunction with DCM is linked to compromised vascular smooth muscle cell and endothelial cell function **(4)**.

Progression of diabetic cardiomyopathy

The majority 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).**

 Similar to those associated with obesity and type 2 diabetes, abnormalities in diastolic filling are characterized by structural and metabolic disturbances that eventually result in a reduction in ventricular wall compliance and impairment of the left ventricle's passive filling phase. 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 follow :

Early stage

In the early stage of diabetic cardiomyopathy, Metabolic disorders including insulin resistance and hyperglycemia do not correspond with significant alterations in myocardial structure and systolic function**.** However, impaired myocardial relaxation can be detected by echocardiography and MRI.

Excessive consumption of refined carbs and fats (the so-called Western diet) has been linked, in mouse studies, to altered insulin signaling, and systemic insulin resistance and impaired of diastolic relaxation, without demonstrating any signs of systolic dysfunction **(2)**.

This impaired diastolic relaxation was characterized as slow initial and peak filling rates as assessed by cine MRI **(2)**.

These impairments were also evidenced by abnormal echocardiographic diastolic parameters, including long period of isovolumic relaxation , abnormal myocardial performance index and impaired septal annular wall motion **(26).**

The earliest finding of diabetic cardiomyopathy include reduced early diastolic filling and increased atrial filling, as well as increased heart stiffness and poor relaxation **(8).**

Impaired insulin signalling also causes a decrease in myocardial blood flow reserve that can be detected by various imaging techniques **(26).**

Advanced stage

Numerous cellular alterations (impaired autophagy of cells that have undergone death by apoptosis and/or necrosis, oxidative stress, and maladaptive immune response) increase cardiac fibrosis in the advanced stage of diabetic cardiomyopathy. This leads to significant changes in diastolic function (initial changes) and systolic function (later in the process) **(27).**

Late stage

The development of myocardial fibrosis, alterations in metabolism, and neurohumoral activation all worsen coronary microcirculation, diastolic and systolic function in the latter stages of diabetic cardiomyopathy**(28).**

Numerous studies have reported that impaired myocardial insulin signalling leads to reduced activation of endothelial nitric oxide synthase and reduced levels of bioavailable nitric oxide **(2)**.

Elevations in oxidative stress promote the breakdown of this molecule and compound the drop in nitric oxide. Decreases in bioavailable nitric oxide and increases in ROS and inflammation promote the deposition and crosslinking of interstitial collagen, which is linked to interstitial fibrosis and impaired myocardial relaxation **(2)**.

For example, in conjunction with impaired insulin signaling, activation of the profibrotic TGF-β1–SMAD signaling pathway increases the concentration of collagen and fibronectin in the heart as well as interstitial fibrosis **(2)**.

Cardiomyocyte necrosis, progressive loss of muscle fibrils, collagen formation in connective tissue, interstitial or perivascular fibrosis, hypertrophy, thickened and sclerotic small coronary vessels, thickening of the basement membrane, hyaline arteriolar sclerosis, and capillary micro aneurysms are among the structural abnormalities linked to diabetic cardiomyopathy **(29).**

Stage	Pathophysiological events	Changes in structure and morphology	Functional performance
Early	Hyperglycaemia; downregulation of GLUT4; increases in free fatty acid levels; insulin resistance; impairment of Ca^{2+} homeostasis; activated sympathetic nervous system	Very small pathophysiological changes in myocytes; normal left ventricular mass and wall thickness	Little or no LVDD
Advanced	Cardiomyocyte injury and death; fibrosis; activated RAAS; maladaptive inflammatory response	Increased left ventricular mass, wall thickness and size	Impairment of left ventricular diastolic function and slightly decreased ejection fraction
Late	Myocardial fibrosis; abnormal coronary microvascular; severe neurohumoral activation; inflammatory response	Substantial increases in left ventricular mass, wall thickness and size	Impairment of both diastolic and systolic function

Table 1 Progression of diabetic cardiomyopathy **(2)**.

GLUT4, glucose transporter 4; LVDD, left ventricular diastolic dysfunction; RAAS, renin–angiotensin–aldosterone system.

Diagnostic markers

ECG

Patients with DCM have altered cardiac electrophysiology, including prolonged QT intervals, the increase of QT dispersions, and T peak-Tend dispersions. The asynchronous cardiac movement is represented by these repolarization anomalies, which have been observed to indicate LVDD **(30) .**

Serum markers

In terms of clinical diagnosis and treatment, a few novel markers seem to hold promise. Major role for fibrotic markers. Diastolic dysfunction (DM-DD) has been linked to elevated levels of active MMP-9 and MMP-7 as well as a decreased TIMP-1/active MMP-9 ratio.Additionally, it was discovered that in early T2D, serum PIP level was negatively

correlated with A-Ar (estimated passive diastolic function), indicating that fibrosis may actually be the root cause of diastolic dysfunction. A few more indicators have also been investigated. A stress response cytokine called GDF-15 is markedly correlated with E/e' (diastolic function index) and is high in asymptomatic DCM **(31)**   .

IGFBP-7 is anticipated to serve as a marker for DCM because it gradually increase in individuals with DM, DM-DD, and DM-SD (systolic dysfunction), but it did not rise in individuals with DD who did not have diabetes. Some claim that more than one serological marker is required to diagnose DCM, indicating that more than one marker may be required. A few investigators had started their efforts. According to a study, DCM could not be diagnosed based on the AUCs of IL-6, TNF-a, and AGEs, which were 0.905, 0.845, and 0.807, respectively **(32).**

But when these biomarkers were combined, the AUC jumped dramatically to 0.924, with a sensitivity of 84.8% and a specificity of 88.2%. The combination of insulin, AGEs, TNF-a, and creatinine aided in the diagnosis of DM-DD (specificity 100%, AUC 0.913). However, with an AUC of 0.795 and a sensitivity of 90.6%, the combination of AGEs and IL-6 was found to be useful for further differential diagnosis of DMSD and DM-DD. This was much better than that of a solo diagnosis **(32).**
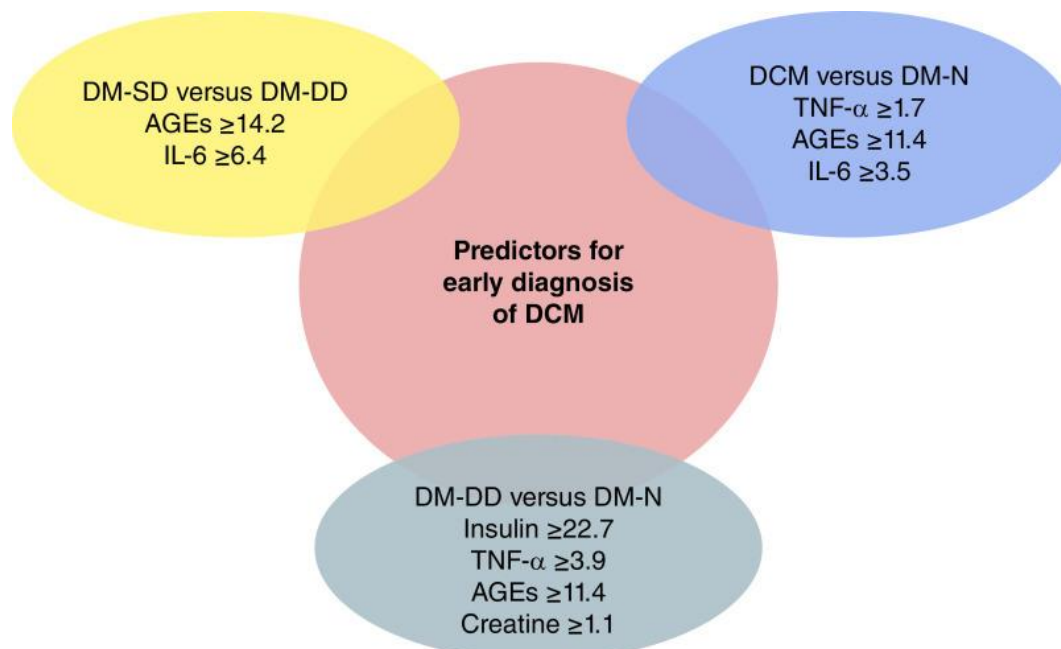

Figure 2 : predictors for early diagnosis of DCM **(32).**

Echocardiography

Echocardiography is a diagnostic technique that is reasonably priced and useful for evaluating both structural and functional heart problems. The most popular method for assessing LV diastolic function is the transmitral Doppler **(4).**

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Myocardial tissue velocities during the cardiac cycle are measured by tissue Doppler imaging (TDI), which can be used to quantitatively quantify regional and global diastolic and systolic myocardial functions. Compared to transmitral Doppler, TDI is a more precise and sensitive diagnostic technique for identifying DCM **(4).**

Traditionally, Doppler echocardiography is used to assess mitral inflow velocity curves and measure LV size in order to diagnose and classify the degree of LV diastolic dysfunction. **(33).**

The American Society of Echocardiography recently updated their recommendations for evaluating LV diastolic function, which now includes parameters such as mitral annular e' velocity, E/e' ratio, LA maximum volume index, and the initial recommended approach of using the mitral inflow E/A ratio. If a patient has clinical symptoms of heart failure with an E/A ratio ≥ 2 measured by Doppler echocardiography, the diagnosis of LV diastolic dysfunction should be established. However, in young individuals, an E/A ratio > 2 can be a normal variant, so it is important to look for other symptoms and signs of heart failure. **(33).**

 For patients with a mitral inflow E/A ratio between 0.8 and 1.9, or with a ratio ≤ 0.8 combined with peak E velocity > 50 cm/s, LA volume index (LAVI) > 34 mL/m2 , peak velocity of tricuspid regurgitation > 2.8 m/s measured by CW Doppler echocardiography, and mitral average E/e' ratio > 14, further confirmation is needed to determine the elevated LV filling pressure and diagnose LV diastolic dysfunction in this patient group**(33).**

Recent developments in 2D speckle tracking echocardiography have allowed for the addition of new parameters to assess LV diastolic dysfunction, such as an LA contractile strain rate < −1.66/s, which indicates decreased LA pump function and improves the accuracy of LV diastolic dysfunction diagnosis in patients with diabetic cardiomyopathy **(33).**

Cardiac CT

Cardiac CT primarily assesses anatomic remodeling, such as dilated LA or dilated LV, in patients with LV diastolic dysfunction, as opposed to 2D echocardiography, which can assess LV diastolic functional parameters, such as the E/A ratio, E/e', etc., to diagnose and classify the degree of LV diastolic dysfunction. A prior study shown that increased LA pressure resulting in LA enlargement would be mediated by high-degree LV diastolic dysfunction **(34)** **.**

The study of **Kaiume, M et al.(35)** showed that a maximum anteroposterior diameter/maximum medial diameter of the thorax > 0.165, a maximum anteroposterior diameter of the LA > 43.9 mm, and a maximum transverse diameter of the heart can be the indicators for LV diastolic dysfunction**.**

Clinically, DM patients with enlarged LA should be evaluated for DM cardiomyopathy. Furthermore, the global LA function is measured by the LA total emptying fraction (LATEF), as is well known. Lessick, J. et al.'s study shown that LATEF < 40%, identified by cardiac CT, provides additive value to echocardiography-derived diastolic dysfunction and can reliably diagnose advanced left ventricular diastolic dysfunction**(36).**
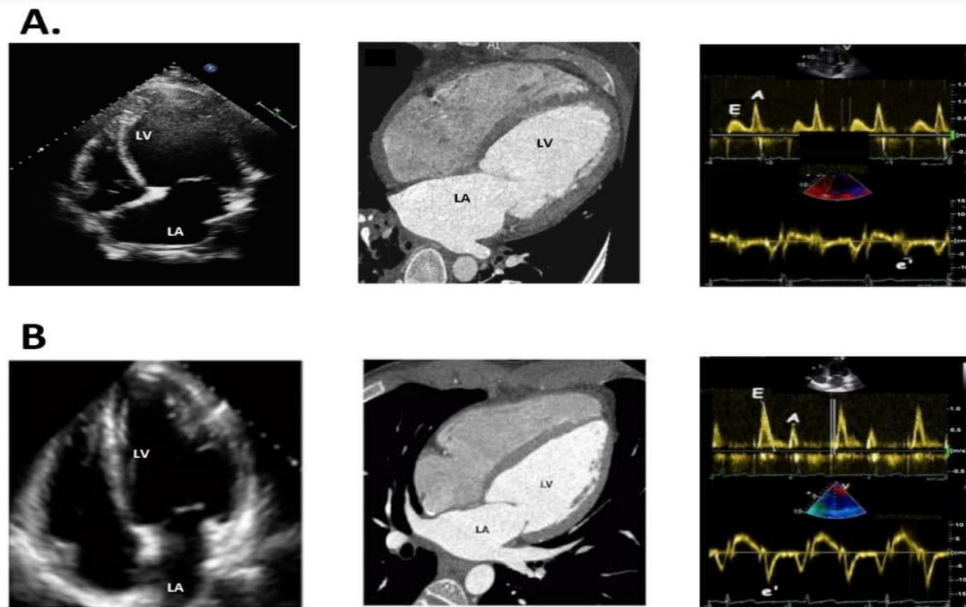

Figure 3 : Diabetes mellitus (DM) cardiomyopathy mediates left ventricular (LV) diastolic dysfunction and dilated left atrium (LA), becoming heart failure with preserved ejection fraction (HFpEF) clinically. Panel (A) represents DM cardiomyopathy with dilated LA and LV diastolic dysfunction including marked decreased early (E)/late (A) mitral flow velocity ratio and marked increased E/mitral annular e' velocity ratio, measured by echocardiography and cardiac computed tomography (CT). Panel (B) represents a normal heart with normal size of LA and normal LV diastolic function with E > A, measured by echocardiography **(33).**

Cardiac MRI

When it comes to diagnosing heart muscle disorders like amyloidosis and Fabry disease, cardiac MRI is a highly useful tool. As of right now, cardiac MRI is the gold standard method for determining LV mass and volumes since it is more reproducible than echocardiography**(37).**

In addition, a recently developed cardiac MRI golden angle method allows the acquisition of 150 to 250 frames per cardiac cycle to match that of echocardiography, which can also measure the mitral inflow and pulmonary inflow velocities by phase-contrast MRI to diagnose the LV diastolic dysfunction. As we know, Doppler echocardiography and tissue Doppler imaging can measure the mitral inflow velocities and myocardial velocities to

classify the degree of LV diastolic function**.** Myocardial velocities can also be measured with phase contrast cardiac MRI. In patients with left ventricular diastolic dysfunction, cardiac MRI-derived mean e' and E/e' have continuously demonstrated excellent concordance with the values from Doppler echocardiography and tissue Doppler imaging **(38).**

One of the main indicators of increased LV filling pressures in patients with severe LV diastolic dysfunction is progressive enlarged LA. When comparing LA size measurements to echocardiography, cardiac magnetic resonance imaging (MRI) yields a more precise result and can accurately assess LA ejection fraction (LAEF). LV diastolic dysfunction is linked to decreased LAEF, decreased LA reservoir, booster pump strains, and increased LA volumes **(39) .**

Different from cardiac CT, cardiac MRI has the capability to detect both focal myocardial fibrosis using late gadolinium enhancement (LGE) and diffuse interstitial fibrosis through parametric mapping sequences by using native T1 and extracellular volume quantification **(33).**

Nuclear Imaging

 The rapid advancement of nuclear medicine equipment and the broad availability of novel radiopharmaceutical agents, attention has also turned to neurohormonal and molecular pathophysiologies. Studies using cardiac sympathetic neuroimaging have discovered that diabetic patients had lower 123I-MIBG-derived radioactivity than controls **(40).**

 It was also shown that cardiac automatic neuropathy was an independent risk marker for the presence of LV diastolic dysfunction in patients with DM. The activation of the sympathetic nervous system contributes to LV diastolic dysfunction. Early diagnosis and treatment of cardiac automatic neuropathy are advocated for preventing LV diastolic dysfunction in patients with DM cardiomyopathy **(40).**

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