Review article

DIABETIC CARDIOMYOPATHY: INTERSECTION OF MACROVASCULAR AND MICROVASCULAR DISEASE, OR MUCH MORE?

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Abstract

Cardiovascular disease is responsible for over 75% of deaths in diabetic patients, the majority caused by coronary artery disease (CAD) and heart failure. Cardiovascular morbidity and mortality in diabetic patients might be independently associated with other pathophysiologic mechanisms than coronary artery disease, epicardial and microvascular disease. There is an increasing notion that diabetic patients suffer from an additional cardiac condition named "diabetic cardiomyopathy". There are several clinical, experimental, pathological and epidemiological researches that support the existence of a specific "diabetic cardiomyopathy". This is assumed to be influenced by complex interaction of several metabolic changes that leads to both functional and structural alterations of the diabetic myocardium. In this review epidemiological aspects and clinical implications of this condition are presented.

Keywords: diabetic cardiomyopathy, diagnosis, treatment

Diabetes and cardiovascular risk

Diabetes is a well-known risk factor for the development of coronary artery disease (CAD) and also for sudden cardiac death [1,2]. It has been considered as CAD equivalent, placing the diabetic patients in the high-risk population for cardiovascular events. The most common cause of death in diabetes is cardiovascular disease, including heart failure, and amongst those with heart failure diabetes is an adverse prognostic marker. The prevalence of HF is around 22% in patients with DM type 2. Diabetic men have more than twice increased risk of heart failure than non-diabetic, while diabetic women have a fivefold increased risk of developing heart failure [1]. This excessive risk of heart failure persists despite correcting for age, hypertension, obesity, hypercholesterolemia, and coronary artery disease. Asymptomatic patients with diabetes type 2 initially are in

the stage A of heart failure (absence of symptoms and structural heart abnormalities), which could potentially progress to stage B and stage C as clinically manifested heart failure, depending on early diagnosis and diabetes control [3-5].

Diabetic patients have 2-4 fold increased risk for fatal and non-fatal CAD [6-10]. Furthermore, despite a comparable infarct size, diabetic patients have a far greater risk of developing HF post-MI compared with nondiabetic patients [11-13]. Patients with diabetes mellitus type 2 have diffuse CAD, more often multivessel disease, increased incidence of silent myocardial ischemia and larger myocardial infarction with poor collateral vessels development. Heart failure due to coronary artery disease in these patients is caused by myocardial ischemia, hibernation and myocardial necrosis. Microangiopathic changes in the small vessels of the heart of diabetic patients may contribute to diabetic cardiomyopathy as well. Less appreciated is the fact that an increase in left ventricular mass is observed in diabetic patients. This is seemingly unrelated to the extent of coronary artery disease. Many patients with diabetes have associated hypertension (28-68%), so that some of the left ventricular hypertrophy common in diabetics is likely related to high blood pressure.

When hypertension is superimposed on the diabetic state, significant myocardial morphologic damage is intensified, producing a powerful substrate for the development of heart failure. Diabetic women tend to have much greater left ventricular mass, and increased left ventricular wall thickness and chamber size. Other abnormalities noted in human diabetic hearts include microvascular constriction, interstitial fibrosis, and edema. In clinical practice, it is difficult to separate out the mutual role of hypertension and ischemia in the development of diabetic cardiomyopathy. Studies have shown that diabetics with hypertension have greater interstitial connective tissue deposition comparing to patients with either diabetes or hypertension as isolated entities, and concomitant hypertension further increases the development of necrotic cell death in myocytes and endothelial cells but does not increase apoptosis [14,15]. These differences are attributed to increased angiotensin II receptor and to oxidative stress in diabetic hearts.

It is proved and clinically known that the major cardiac complications of diabetes mellitus include large coro-

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nary conduit arteries, epicardial coronary arteries, and the microvasculature. What is less considered and still controversial by some cardiologists is the concept that diabetes mellitus affects cardiac structure and function independent of high blood pressure or coronary artery disease (CAD). There are many experimental, pathological, epidemiological, and clinical studies that underline the existence of "diabetic cardiomyopathy". The Framingham study demonstrated the increased incidence of congestive HF independent of age, hypertension, obesity,

CAD and hyperlipidaemia. Considering the increasing incidence of diabetes mellitus and its strong association with the development of heart failure, it is important to have in mind the evidence concerning the concept of "diabetic cardiomyopathy", which was first described nearly 30 years ago [14]. We have to understand the basic mechanisms leading to diabetic cardiomyopathic changes in order to treat these patients at early phases of the disease.

Fig. 1. Myocardial perfusion scintigraphy- SPECT scan with Tc-99m sestamibi. Mild reduction of radiotracer accumulation in the inferior wall, inferoseptal and small region of anteroseptal wall in both studies. Shortened septum. There are no signs of stress inducible ischemia. Increased left ventricular volumes with reduced global left ventricular function. Mild global hypokinesia. Scan results indicate cardiomyopathic changed myocardium in patient with DM type 2

Pathophysiology of diabetic cardiomyopathy

Diabetic cardiomyopathy is described as a disease process which affects the myocardium in diabetic patients causing a wide range of structural abnormalities that lead to left ventricular (LV) hypertrophy, and a combination of diastolic and systolic dysfunction. The condition is associated with structural and functional myocardial dysfunction not related to the presence of coronary artery disease (CAD), congenital heart diseases, valvular heart diseases or hypertension. The concept of diabetic cardiomyopathy is based on the concept that diabetes is the factor which causes changes at the cellular level, leading to structural myocardial abnormalities. Several pathological mechanisms have been described and connected with the pathogenesis of diabetic cardiomyopathy. Initial metabolic processes are postulated as triggers of mechanistic changes in myocardial structure, calcium signaling pathways and metabolism which may precede clinical manifestations of cardiac dysfunction. The other im-

portant factors include abnormalities in free fatty acid metabolism, increased oxidative stress, increased apoptosis, activation of the RAAS, autonomic neuropathy and, rarely, derangements in copper metabolism (Figure 1). Patients with hypertension and CAD may well have myocardial changes related to these disease processes, but a specific cardiomyopathy may also affect the myocardium secondary to diabetes causing a synergistic adverse effect as seen with a combination of diabetes and hypertension. The challenging clinical question is whether there are linking pathways between strict metabolic changes and coronary artery disease that cause cardiovascular complications and heart failure in more than 75% of diabetic patients.

Diabetes mellitus and heart failure have multiple common subcellular mechanisms that can be followed at different stages of impaired glucose tolerance and insulin resistance. Hyperglycemia is a causative factor that induces maladaptive mechanism, which leads to heart failure. Diabetic cardiomyopathy was originally descry-

The diagram illustrates the pathogenesis of Diabetic Cardiomyopathy (DCM). It shows a cell membrane with GLUT transporters and a signaling pathway involving PDK4, Sirtuin, and MCoA. Hyperglycemia leads to decreased GLUT expression and glucose uptake, impaired insulin signaling, and increased PKC and AGE. These factors lead to ROS production, which causes glucotoxicity, fibrosis, and mitochondrial dysfunction. The final outcome is Cardiac Dysfunction (CD) and Diabetic Cardiomyopathy (DCM).

ETES

↑ FFAs and TG

↑ FA uptake

CD36

Cardiac lipid accumulation

↑ FA oxidation genes

Ceramide

ROS

↑↑ FA oxidation

CPT1

mitochondrial uncoupling / ↓ CPT1

Lipotoxicity

mitochondrial dysfunction

MYOPATHY

Diabetic cardiomyopathy consists of two major components, the first being a short-term, physiological adaptation to metabolic alterations, and the second represents degenerative changes for which the myocardium has only a limited capacity for repair. However, many factors such as treatments, metabolic characteristics, lipid profile, and other individual differences may affect the process of development of diabetic cardiomyopathy, and not all diabetic patients are affected by the same factors or to the same degree, which may result in marked variability in the clinical presentation of the diabetic cardiomyopathy. Obesity, especially abdominal obesity is an independent risk factor for heart failure. Obese patients have increased myocardial collagen content and increased sympathetic function. Human adiposities seem to be capable of secreting a cardio-active substance that is negatively inotropic. One of the agents is leptin. Increased level of leptin is seen in obesity. The effects of long-term increased levels of leptin on cardiomyocytes include structural and metabolic changes, which have mitogenic effect, myocardial hypertrophy and cardiomyocyte fatty acid loading. Increased levels of intracellular

In the course of diabetic cardiomyopathy, a spectrum of myocardial abnormalities develop and progress which include LVH and diastolic and systolic dysfunction. Left ventricular hypertrophy (LVH), systolic and diastolic dysfunction have distinct prognostic implications in the context of diabetic cardiomyopathy. The presence of LVH on the ECG is a poor prognostic indicator as seen by the results of the Framingham study [16]. The presence of LVH has been linked with increased markers of systemic inflammation [fibrinogen and CRP (C-reactive protein)] and microalbuminuria and, in a study of 1299 type II diabetic patients, increased albuminuria was a marker of endothelial damage and increased atherothrombotic risk [17].

In the context of diabetic cardiomyopathy, systolic dysfunction occurs late, often when patients have already developed a significant diastolic dysfunction. The prognosis in patients with depressed systolic dysfunction is poor with an annual mortality of 15-20%.

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Little work has been done to assess the prognosis of asymptomatic isolated diastolic dysfunction, but there is one study which shows that echocardiographic evidence of subclinical contractile dysfunction and diastolic filling abnormalities are both predictive of subsequent CHF (chronic HF) [18]. Patients with diastolic HF have a significantly increased mortality of 58% annually compared to 1% for aged-matched controls [19].

Hyperglycemia, hyperlipidemia and increased ROS (reactive oxygen species) induce alterations in downstream transcription factors which result in changes in gene expression, myocardial substrate utilization, myocyte growth, endothelial function and myocardial compliance. Hyperglycemia may mediate its damaging effects through a series of secondary transducers. One of the principle abnormalities is the excess generation of AGEs (advanced glycation end-products), which deactivate NO (nitric oxide) and impair coronary vasodilation. Sustained hyperglycemia causes excess formation of mitochondrial ROS, which affects transcription, leading to contractile dysfunction [20,21]. An increase in ROS decreases NO levels, which leads to myocardial inflammation and endothelial dysfunction via PARP [poly (ADP-ribose) polymerase] [22]. The severity of diastolic dysfunction correlates with HbA1c (glycated hemoglobin) levels and the likely cause is AGE induced formation of ROS, resulting in myocardial collagen deposition and fibrosis [23-25].

Independent of the effects of hyperlipidemia on coronary artery endothelial function, the increase in and dependence of diabetic myocardium on fatty acid supply results in several major cellular metabolic perturbations. Impaired glycolysis, pyruvate oxidation, lactate uptake and a greater dependence on fatty acids lead to a perturbation of myocardial bioenergetics and contraction/relaxation coupling [26]. Recent data from animal and human experimental studies have demonstrated the significant role of rennin angiotensin aldosterone system (RAS) in diabetes-induced myocardial dysfunction [27]. Hyperglycemia activates intra-cardiac RAS that has various effects on the myocardial cells. Intracellular angiotensin levels are assumed to be 3.4-fold higher in the cardiomyocytes of diabetic compared to nondiabetic patients [27].

Increased activation of the DAG (diacylglycerol)-activated PKC signal transduction pathway has been shown to induce many of the changes in diabetic cardiomyopathy which include a reduction in tissue blood flow, enhanced extracellular matrix deposition, capillary basement membrane thickening and increased vascular permeability with alterations in neovascularization. An inadequate angiogenic response to ischemia in the myocardium of diabetic patients could result in poor collateral formation and hence an increased propensity to infarction with a reduced reparative response.

Endothelial dysfunction is a precursor to and an effect of atherosclerosis. Anatomical and functional abnormalities of the vascular endothelium are commonly associated with diabetes [28]. The clinical implications of

endothelial dysfunction are not limited to increased atherosclerosis. Endothelial cells also help collateral circulation development, which is reduced in patients with diabetes and may explain the increased infarct extension and congestive HF after MI in these patients.

The increased angiotensin II in diabetic myocardium and lipid metabolism abnormalities in diabetes may play a central role in early atherogenesis and progression to atherosclerotic plaque. Insulin resistance is also associated with accelerated atherosclerosis, especially coronary heart disease.

It is well known that hypertension and diabetes lead to a rise in arterial stiffness through endothelial dysfunction-mediated fibrosis [29]. Vinereanu *et al.* demonstrated an association between conduit arterial stiffness and impaired LV function. Their results suggest that subendocardial function of the left ventricle may be depressed in patients with stiff and relatively noncompliant conduit arteries [30]. The net effect of these hemodynamic changes is ischemia, especially in the subendocardium, which, if chronic, can lead to interstitial fibrosis and the development of HF [31].

Cardiac autonomic neuropathy (CAN) may contribute to impaired diastolic function and is associated with an increased cardiovascular risk in diabetic patients. Diabetic autonomic neuropathy is associated with an impaired vasodilator response of coronary resistance vessels to increased sympathetic stimulation. Sympathetic dysfunction has been related to both systolic and diastolic dysfunction in type II diabetes [32]. Extremely high mortality rates have been associated with clinical findings of diabetic autonomic neuropathy.

Oxidative stress caused by toxic molecules may play a critical role in subcellular remodeling and abnormalities of calcium handling that lead to subsequent diabetic cardiomyopathy. Alterations in regulatory proteins and contractile proteins may be important contributors to abnormal myocardial carbohydrate and lipid metabolism in diabetes [33].

Structural and functional alterations of the small vessels in diabetes have been incriminated in the development of diabetic cardiomyopathy, although this remains controversial. There are studies indicating that abnormality of cardiac function described in diabetes is not associated with thickening of the myocardial capillary basal lamina [34]. According to Larghat's study, which used magnetic resonance imaging, patients with diabetes have increased left ventricular mass and torsion, and decreased perfusion reserve. Despite these findings, it has been proposed that such focal changes in microvessels are insufficient to account for the diffuse myocardial degeneration with interstitial fibrosis in diabetic cardiomyopathy.

Diagnostic algorithm in patients with suspected diabetic cardiomyopathy

Diagnosis of DCMP requires establishment of impaired glucose metabolism and clinical approach to exclude

other causes of LV dysfunction: CAD, valvular disease, hypertension, congenital heart disease and infections such as viral myocarditis or toxins-induced, familial or infiltrative cardiomyopathies [35]. The following risk factors which might exacerbate DCMP need special attention: obesity, chronic high blood glucose, high blood pressure, dyslipidemia, smoking and alcohol consumption. The diagnostic should include a detailed

history and a proper physical examination: urine analysis to test for the presence of proteinuria, stress test, chest X-ray, electrocardiography, echocardiography, myocardial perfusion SPECT imaging (Table 1). Invasive measures should also be considered in some situations including myocardial biopsy, cardiac catheterization to evaluate cardiac chamber blood flow, pressures and coronary blood flow.

Table 1. Diagnostic approaches used in the diagnosis of diabetic cardiomyopathy

Diagnostic methods	Parameters and clinical implications
Clinical	History of DM and family history of diabetes Physical examination, evaluation of symptoms and complications
Laboratory	Urine, for proteinuria Serum aminoterminal propeptide of type I and type III collagens B-natriuretic peptide (BNP), for increased ventricular pressure or heart failure
Transthoracic echocardiography	Evaluation of diastolic LV function (Transmitral Doppler analysis, for left ventricular mass and diameter; pulmonary venous blood flow), TDI, decreased tissue velocities for both diastolic and systolic dysfunction 2D/TDI, strain and strain rate, for systolic and diastolic dysfunction Evaluation of systolic LV function
Magnetic resonance imaging	MRI, for left ventricular mass and diameter Late gadolinium enhancement MRI, for diastolic and systolic dysfunction Magnetic resonance spectroscopy, for myocardial fibrosis, triglyceride content and myocardial phosphocreatine to ATP ratio
Myocardial perfusion SPECT	G-SPECT, differentiate ischemic from non-ischemic cardiomyopathy, assess both myocardial perfusion and ventricular function Quantitative myocardial perfusion SPECT, myocardial and coronary artery disease
PET	Radiotracer kinetics, quantitative assessment of myocardial blood flow

SPECT- single photon emission tomography; PET- positron emission tomography

Left ventricular dysfunction

Left ventricular (LV) diastolic dysfunction is the earliest manifestation in DCMP, which may evolve to symptomatic heart failure [36-37]. Doppler echocardiography imaging has emerged as an important non-invasive measure, which could easily reveal diastolic and systolic abnormalities [38]. The diastolic dysfunction in DCM is characterized by an increased ventricular wall stiffness and longer diastolic relaxation time, commonly at an early stage of the disease course.

Left ventricular systolic dysfunction is the later manifestation of the LV functional impairment continuum. There has been discrepancy regarding early detection of LV systolic dysfunction using left ventricular ejection function (LVEF) and LV fractional shortening (LVFS), attributable to load dependence and the relative insensitivity of LVFS in detecting subtle features of LV systolic dysfunction [39]. Currently, the more sensitive echocardiographic indices used to evaluate early LV systolic function include TDI and speckle tracking echocardiographic strain rate imaging which detect subclinical LV systolic dysfunction in DM [39].

Echocardiography

2D-TTE is unable to detect the subtle changes in myocardial function in DM. Newer technologies, such as TDI, look promising as they enable an assessment of myocardial tissue velocities with relative ease. Strain and strain rate echocardiography is a unique technique for assessing myocardial systolic and diastolic function. It is a new advanced imaging tool which is highly sensitive and reproducible to evaluate early and subtle impairment of LV function.

Magnetic resonance imaging

Cardiac MRI is a useful imaging tool for assessment of structural and functional myocardial disorders. Gadolinium-enhanced cardiac MRI has been useful in predicting major adverse cardiac events in diabetic patients with no prior history of ischemic heart disease.

Stress single-photon emission computed tomography

Stress single-photon emission computed tomography (SPECT) is a validated imaging tool providing information on the physiological significance of flow-limitation and sarcolemmal membrane integrity. LV function analysis by SPECT enhances its prognostic and diagnostic ability, particularly in the prediction of cardiac death. Reliable automatic algorithms of SPECT provide semi-

quantitative assessment of myocardial perfusion, LVEF, LV volumes, regional myocardial wall motion and thickening. It also has high sensitivity in differentiating ischemic

from non-ischemic cardiomyopathy. Nevertheless, factors other than CAD could play a role in the pathogenesis of myocardial dysfunction in diabetic patients, including endothelial dysfunction, interstitial fibrosis, impaired modulation of vascular growth and remodeling. As a result, SPECT could be helpful in these situations.

Positron emission tomography

Among the available imaging modalities, only positron emission tomography (PET) allows quantitative assessment of myocardial blood flow using radiotracer kinetics. PET provides a high spatial resolution detection of myocardial metabolic abnormalities and currently represents the most valuable imaging analysis for diagnosis and prognosis in DM.

Therapeutic options and clinical implications

High prevalence of CAD and cardiovascular complications in diabetic patients are cause of great concern and main treatment force in daily cardiology practice. The existence of specific diabetic cardiomyopathy is scientifically proved and is present, which urges us to think more carefully on metabolic changes that precede a disease and lead to long-term functional impairment. Strict metabolic control of glucose levels and all risk factors together with early screening for diabetes in high-risk population is most probably the way we should act in order to limit or postpone development of diabetic cardiomyopathy. Management approach should be aimed at CV prevention. This includes changes in lifestyle, improvement of diabetic control, lipid lowering therapy, management of coexistent hypertension and CAD if present, and management of heart failure with preserved and eventually reduced LVEF. Improvement of glycemic control (with HbA1c <7%) has been shown to be associated with lower diabetic microvascular complications, which has important pathogenic role in the development of DCMP. Additional development of hypertension and CAD should be treated based on latest disease guidelines.

The European Society of Cardiology and the European Association for the Study of Diabetes recommend ACE inhibitors (or Angiotensin-II-receptor-blockers) and Beta-blockers as first line therapy for patients with heart failure and diabetes (Class I, Level C). Diuretics are beneficial for symptomatic treatment of patients with heart failure. Great trials (SAVE, ATLAS, CONSENSUS, GISSI 3) have shown ACE inhibitors to be important in reduction of cardiovascular mortality and improvement of quality of life. Recommendation for the use of beta blockers is based on the results of diabetic subgroups

in studies such MERIT-HF, CIBIS II, COMET and COPERNICUS [40,41].

Conclusions

In this review we present data that support the existence of diabetic cardiomyopathy as a distinct clinical entity. The pathophysiology of the condition still remains questionable, but includes interstitial fibrosis, cardiomyocyte loss, impaired energy utilization, small vessel disease, and neuropathy. Functional consequences of the above changes include diastolic and systolic dysfunction, which may manifest as dyspnea and exercise intolerance. Risk factors such as hypertension, atherosclerosis, and dyslipidemia are common in diabetic patients and further compromise cardiac status. Currently, no specific therapeutic strategies can be recommended for diabetic cardiomyopathy. Management of traditional risk factors and lifestyle modification established in the treatment of cardiac disease should be intensively applied. Further research of the molecular basis of diabetic cardiomyopathy is needed in order to introduce more appropriate therapies for these patients

Conflict of interest statement. None declared.

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