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Is diabetic cardiomyopathy a specific entity?

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Abstract

Diabetes mellitus (DM) is characterised by hyperglycemia, insulin resistance and metabolic dysregulation leading to diastolic and systolic dysfunction in diabetes. In this review, the pathogenetic and pathomorphological changes leading to diastolic and systolic dysfunction in diabetes are discussed. Changes in metabolic signalling pathways, mediators and effectors contribute to the pathogenesis of cardiac dysfunction in DM called diabetic cardiomyopathy (DC). Echocardiographic studies report on the association between DM and the presence of cardiac hypertrophy and myocardial stiffness that lead to diastolic dysfunction. More recently reported echocardiographic studies with more sensitive techniques, such as strain analysis, also observed systolic dysfunction as an early marker of DC. Depression of systolic and diastolic function is continuum and the line of separation is artificial. To conclude, according to current knowledge, DC is expected to be a common single phenotype that is caused by different pathogenetic and pathomorphological changes leading to diastolic and systolic dysfunction in diabetes.

Key words: Diabetes mellitus; Diabetic cardiomyopathy; Pathogenesis; Diastolic dysfunction; Systolic dysfunction; Morphological changes; Apoptosis

Core tip: Changes in metabolic signalling pathways *via* several mediators contribute to the pathogenesis of cardiac dysfunction in diabetes called diabetic cardiomyopathy (DC). In this review, the pathogenetic and pathomorphological changes leading to diastolic and systolic dysfunction in diabetes are discussed. Echocardiographic studies report on the association between diabetes and the presence of cardiac hypertrophy and myocardial stiffness that lead to diastolic dysfunction. More recently reported echocardiographic studies with more sensitive techniques, such as strain analysis, also observed systolic dysfunction as an early marker of DC.

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INTRODUCTION

Since 1972, when Rubler *et al*[1] described 4 diabetic patients with congestive heart failure and normal coronary arteries, our knowledge of the observed pathomorphological changes of the heart called diabetic cardiomyopathy (DC) has gradually increased[2,3]. However, the patohistological changes in DC are not specific[1-3]. DC has been defined as ventricular dysfunction that occurs independently of hypertension and coronary artery disease (CAD)[2]. The prevalence of DC is estimated to 60% in well-controlled type 2 diabetic patients[4,5]. The most useful method for the detection of DC is echocardiography that usually describes cardiac hypertrophy and diastolic dysfunction[4,5]. DC is a poorly understood entity, however, some mediators leading to abnormalities in myocardial structure, ventricular dysfunction and heart failure have been reported so far[6]. Patients with diabetes mellitus (DM) are at high risk for developing heart failure[6]. The spectrum of heart failure syndrome in DC is also not precisely defined despite the usually used definition

of DC as a diastolic heart failure with normal ejection fraction. Anyhow, in different patients several different associated risk factors are observed, such as hypertension and adiposity or associated clinical entities, such as CAD, small vessel disease, autonomic dysfunction and arrhythmias. All of these entities have a significant influence on myocardial structure and function. In this review, the pathogenesis, as well as the prevalence and potential forms of DC and the question whether DC is either a unique specific cardiomyopathy starting with diastolic dysfunction that eventually leads to ventricular dysfunction and heart failure, are discussed.

PREVALENCE

The prevalence of DM is increasing worldwide due to the increase in population, urbanisation, the prevalence of obesity and physical inactivity. The Framingham Heart study showed that DM increased the risk for heart failure 2.4-fold in diabetic men and fivefold in diabetic women compared with age- and sex-matched control subjects[6]. This risk was independent of hypertension, obesity and CAD. Diabetic patients also have an increased risk for heart failure after myocardial infarction, compared to non-diabetics[7,8]. However, not only patients with DM, but also patients with higher baseline glucose without diabetes have a higher incidence of heart failure[6].

Mainly echocardiographic population-based studies report on the association between DM and the presence of cardiac hypertrophy and myocardial stiffness, independently of hypertension[4,5]. There are basically two pathophysiological processes leading to heart failure in diabetic patients, the first being CAD and the second DC. CAD is increased in patients with DM due to accelerated atherosclerosis associated with risk factors, such as visceral obesity, hypertension, dyslipidaemia, and prothrombotic factors[7,9]. Despite the increased burden of CAD in diabetic patients, the real prevalence of CAD in DM patients is unknown[7,9]. Population -based studies reported on the adverse effect of DM on life expectancy, mainly due to cardiovascular disease and also in patients with heart failure[10].

PATHOGENESIS

Various animal models of DC have proposed several mediators and effectors that are the consequence of altered metabolic signalling pathways and contribute to the pathogenesis of cardiac dysfunction in diabetes.

Hyperglycemia, advanced glycation end pruducts and insulin resistance

DM is characterized by hyperglycemia, hyperinsulinemia, and insulin resistance[11]. The reduced glucose uptake in the diabetic heart as a result of insulin resistance facilitates a substrate shift towards increased fatty acids oxidation, resulting in reduced cardiac efficiency[12]. Epicardial adipose tissue (EAT) that covers 80% of the heart surface and constitutes approximately 20% of the total heart weight have endocrine and paracrine properties that probably interfere with cardiac function. It is speculated that EAT facilitates the development of insulin resistance and cardiac dysfunction[13]. Glucotoxicity has been proposed in animal models as an important element of myocardial dysfunction. Glucose and collagen interact, and form Schiff bases. The fibrous network is reorganised with the so-called Amadori products. A further chemical modification of Amadori products leads to the formation of macromolecules that are labelled as advanced glycation end products (AGEs). AGEs are a stable form of cross-linked collagen that accumulate in vessel walls and in myocardial tissue and increase diastolic stiffness of the heart and contribute to endothelial dysfunction[14]. Higher diastolic left ventricular (LV) stiffness was related to both AGE deposition and interstitial fibrosis[15]. It was observed that serum levels of AGEs correlate with the prolongation of isovolumic relaxation time in patients with diabetes.

Altered substrate metabolism

Metabolic dysregulation in DM also involves fatty acid metabolism. Despite contradictory reports on the level of circulating free fatty acids (FFA), which are elevated in some studies and not in others[16,17], there is a dysregulated lipid signalling that leads to an increased FFA metabolism and accumulation of FFA[18,19]. In parallel, there is a decrease of insulin-mediated glucose uptake. FFA also induced the inhibition of glucose oxidation and resulted in abnormally high oxygen requirements during FFA metabolism. The net result of enhanced fatty acid oxidation and decreased glucose and pyruvate utilization led to the excess of glycolytic intermediates and increased the synthesis of ceramide leading to apoptosis. This process, called gluco-lipotoxicity induced mitochondrial uncoupling, decreased adenosine triphosphate synthesis and mitochondrial dysfunction[20,21]. Changes in substrate dependence lead to impaired systolic and diastolic function due to the perturbation of myocardial bioenergetics and contraction/relaxation coupling[21,22].

Increased oxidative stress

Many studies report oxidative stress as a major common factor in the development of DC, however, the exact mechanisms involved in exacerbated reactive oxygen species (ROS) production are not well understood. Studies proposed insulin resistance and increased mitochondrial fatty acid flux that predisposes cardiac mitochondria to ROS overproduction[23]. In addition to the more important and larger fraction of total cellular ROS that are generated in mitochondria, enzymatic system in cytosol, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is also modulated by diabetes[24]. Increased oxidative stress causes cardiomyocyte cell damage, resulting in programmed cell death-apoptosis and fibrosis[25].

Impaired calcium homeostasis and dysfunction of mitochondria and endoplasmatic reticulum

Oxidative stress exacerbates mitochondrial and endoplasmatic reticulum (ER) dysfunction and produces subcellular remodelling and abnormalities of calcium handling[26]. There is calcium imbalance within the diabetic cardiomyocytes, which is characterized by calcium cytosolic overloading and reduced mitochondrial ATP production. The ER, through negative regulation of insulin's metabolic signalling, additionally impairs calcium homeostasis. There is a release of calcium from the ER into cytosol and reduced activity of the sarcoplasmatic reticulum calcium pump[27]. The consequences of these changes are alterations in the calcium sensitivity of regulatory proteins involved in the regulation of the cardiac actomyosin system, leading to impaired left ventricular function[28]. As an initial dysfunction, researchers observed prolonged diastolic relaxation time, hower later on cardiomyocyte apoptosis due to the formation of mitochondrial permeability transition pore has been observed[29].

Activation of the renin-angiotensin-aldosterone and sympathetic system

Hyperinsulinemia causes overactivation of the renin-angiotensin-aldosterone system[30]. This leads to cardiac insulin resistance and the activation of mitogen activated protein kinases, which promote fibroblast proliferation while inducing cardiomyocyte fibrosis and apoptosis[31]. The serum level of aldosterone is increased in the pre-diabetic and diabetic condition and triggers LV hypertrophy, fibrosis and cardiac remodelling[32]. Both angiotensin Ⅱ and aldosterone cause increased production of ROS and the activation of NADPH oxidase, and they therefore increase cytosolic oxidative stress[33]. Aldosterone also aggravates cardiac fibrosis by triggering pro-inflammatory factors through activation of matrix metalloproteinases and the transforming growth factor β (TGF-β)[34]. There are reports of overactivation of the sympathetic system in the pre-diabetic and diabetic condition that further contributes to metabolic abnormalities. Straznicky observed the association of blunted sympathetic responsiveness and insulin resistance, and disturbed sympathetic neurobiology is characterized by augmented resting sympathetic nervous activity and blunted sympathetic responsiveness to oral glucose ingestion[35].

STRUCTURAL CHANGES

Anatomic changes observed in DC are characterised by myocyte hypertrophy and myocardial fibrosis[2,3]. Beside pathohistomorphological findings, left ventricular hypertrophy, defined as an increase in the left ventricular mass by echocardiography or by magnetic resonance imaging has been reported in DC[2,3].

Fibrosis, necrosis and apoptosis

In DC, fibrosis is attributed to replacement fibrosis caused by myocyte necrosis and to increased interstitial fibrosis. Interstitial fibrosis in DC is driven mainly by increased accumulation of collagen type Ⅲ[3,36]. DC is characterised by accelerated myocyte cell death and accelerated apoptosis[3,36]. The processes of accelerated necrosis and apoptosis are driven by hyperglycemia, accelerated production of ROS, upregulation of the local renin angiotensin aldosterone system, and through modulation of the insulin-like growth factor-1 and the TGF-β1 by angiotensin Ⅱ. Apoptosis does not cause scar formation or accumulation of interstitial collagen, with nuclear fragmentation and cell shrinkage being replaced by the surrounding cells[37]. On the contrary, myocyte necrosis produces the widening of extracellular compartments among myocytes and increased deposition of collagen, resulting in replacement fibrosis and connective cell proliferation[38]. The presence of hypertension in patients with diabetes increases myocyte necrosis 1.4-fold compared to diabetes alone, but it has no influence on apoptosis[39].

Cardiomyocyte hypertrophy

In DC, Huyn and Rosenkrans observed the increase of several markers of cardiomyocyte hypertrophy, including increased cardiomyocyte width and myofiber disarray[40,41]. The loss of cardiomyocytes due to apoptosis and necrosis lead to compensatory hypertrophy of the remaining viable cardiomyocyte. Researchers observed an upregulation of hypertrophic gene expression of β-myosin heavy chain, ANP, and BNP. The causes of the diabetes-induced hypertrophic response are probably hyperglycemia and oxidative stress[40,41].

CHANGES IN CARDIAC FUNCTION

Diastolic dysfunction

A number of echocardiographic studies have characterised functional changes early in the course of DC. Diastolic abnormalities have been reported in 23% to 75% of patients with DM[42-45]. A high variability in the prevalence of diastolic dysfunction raises a question on the implemented methodology. Most of the patients included in these studies were asymptomatic without overt heart disease and their report based on mitral inflow pattern where they observed an increased E/A ratio (where E is mitral peak early-diastolic filling velocity; A is mitral late diastolic filling velocity), prolonged deceleration time, increased isovolumic relaxation time, or described combined indices derived from mitral inflow pattern and pulmonary venous flow[46-48]. Later on, some investigators analysed Doppler tissue imaging diastolic velocities and mitral inflow pattern and reported on their indices, such as E/e' that is non-invasive correlate of left ventricular filling pressure (e' is the early diastolic mitral annular velocity)[45,49]. Ernande reported a 47% prevalence of diastolic dysfunction, with 33% grade I or pattern of impaired relaxation and 14% grade Ⅱ or pseudonormal pattern[50] in patients with DM with normal ejection fraction and controlled blood pressure. Anyhow, most of these studies have been completed before the reliable complex diagnostic algorithm of diastolic function was accepted, and therefore did not allow us a conclusion based on

single parameters[51].

Systolic dysfunction

Although many studies have shown that diabetic patients have abnormal diastolic function but preserved systolic function, this may well be due to techniques used for the evaluation of systolic and diastolic dysfunction. Usually applied techniques are probably more sensitive for diastolic dysfunction than for systolic dysfunction. When thinking of systolic function, we usually think of ejection fraction that depends a lot on radial contractile function, but the longitudinal contractile function of ventricle is primary depressed. Moreover, with the application of more sensitive techniques for the analysis of systolic function, such as strain deformation imaging, researchers observed that the systolic function is impaired despite normal left ventricular ejection fraction. Ernande reported that preclinical radial and longitudinal systolic strain is depressed in 28% of patients with DM with normal diastolic function[50]. This study indicates that systolic strain alteration may exist despite normal diastolic function, or otherwise indicating that diastolic dysfunction should not be considered the first marker of a preclinical form of DC.

Continuum of diastolic and systolic dysfunction

Deterioration of systolic and diastolic function is continuum. There is no separation of diastolic and systolic function in DM, nor in other metabolic cardiomyopathies. Diastolic dysfunction was associated with increased cardiac triglyceride content in the ob/ob mice model of DM[52]. The role of calcium homeostasis studied in the db/db mice model of DM showed increased diastolic sarcoplasmatic reticulum Ca^{2+} leak, reduced synchrony of Ca^{2+} release, lower peak systolic and diastolic Ca^{2+} have, therefore, an influence on both systolic and diastolic function[53]. Abnormality in systolic and diastolic function is also associated with myocardial structural changes. Obviously, there are numerous factors that might have an unfavourable effect on systolic and diastolic function in subjects with DM.

PHENOTYPE OF DC

There is still a debate on how DC should be defined. DC is not an isolated diastolic entity. Due to metabolic abnormalities, we observed systolic and diastolic dysfunctions that are initially subclinical and gradually progress to a full-blown syndrome of congestive heart failure. To conclude, according to current knowledge, DC is expected to be a common single phenotype that is caused by different pathogenetic and pathomorphological changes leading to diastolic and systolic dysfunction in diabetes.

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