Diabetic cardiomyopathy

Diabetic cardiomyopathy (DCP) is defined as ventricular dysfunction in the absence of hypertension, coronary artery and valvular heart disease, which increases the risk of heart failure (HF). Due to better understanding of its pathophysiology and clinical importance, DCP is more frequently recognized in daily practice. The most important mechanisms of DCP are hyperglycemia, insulin resistance/hyperinsulinemia, abnormal fatty acid metabolism, increased apoptosis, cardiac autonomic neuropathy and local renin-angiotensin-aldosterone system (RAAS) overactivation. Echocardiography is the most frequently used diagnostic method for the detection of this pathology. Currently, although there is no specific treatment for DCP, strict glycemic and concomitant risk factor controls seems to be the most important target strategy for prevention of the progression and treatment of DCP. In this article, we aim to provide an extensive review on the pathophysiology, diagnosis, management of DCP.

Key words: Diabetic cardiomyopathy, diastolic dysfunction, echocardiography

Introduction

The global prevalence of diabetes mellitus (DM) is increasing very fast, currently the number of diabetic people is over 300 million and expected to reach close to 500 million within 20 years (1). Cardiovascular diseases are responsible from the three quarters of the deaths among this population (2). Although coronary artery disease (CAD) is very common, heart failure (HF) is also a major cause of mortality and morbidity in patients with diabetes mellitus (3). In addition, diabetic individuals are under increased risk for HF development after adjusting concomitant risk factors such as hypertension and CAD (4, 5). The Framingham study, United Kingdom Prospective Diabetic Study and Euro Heart Failure Survey all suggested that the presence of diabetes may independently increase the risk of developing HF. Up to 75% of patients with unexplained idiopathic dilated cardiomyopathy were found to be diabetic (5).

Diabetic cardiomyopathy (DCP), was first defined by Rubler (6) in 1972, is characterized by the myocardial dysfunction in the absence of CAD, hypertension, or valvular heart disease (6-8).
associated with both type 1 and type 2 DM and presents as by early-onset diastolic and late-onset systolic dysfunction (7, 8). Although it is common, diagnosis of DCP is very difficult. The most frequently used diagnostic methods are echocardiography and cardiac magnetic resonance imaging (MRI) (8, 9). In the early phase of DCP, the pathologic changes can be reversible with strict metabolic control, but in the continuous process the myocardial changes become irreversible and the risk of developing HF increases (10-12). This review focuses on pathophysiology, diagnosis and management of DCP.

Pathophysiology

DCP has been a poorly understood disease and underlying mechanisms are not completely elucidated. Development of DCP includes complex and multifactorial pathophysiological mechanisms. Common pathological changes of diabetic heart are myocyte hypertrophy, interstitial fibrosis and increase in contractile protein glycosylation (5). As a result of these changes, diastolic compliance decrease, ventricle hypertrophies and in the advanced stages systolic functions may worsen (5, 13).

Hyperglycemia and hyperinsulinemia

Hyperglycemia is considered to be a central trigger in the pathophysiology of DCP because it starts several adaptive and maladaptive responses (Fig. 1) (7, 8). Hyperglycemia leads to an increase in oxidative stress by exacerbating glucose oxidation and mitochondrial generation of reactive oxygen species (ROS) which cause DNA damage and contributes to accelerated apoptosis. Also increased ROS activate poly (ADP ribose) polymerase (PARP) as a reparative enzyme (4). PARP inhibits glyceraldehyde phosphate dehydrogenase (GADPH), diverting glucose from its glycolytic pathway and into alternative biochemical pathways that are considered to be the mediators of hyperglycemia-mediated cellular injury. PARP also promotes cardiac damage by activating nuclear factor (NF) κ β and inducing overexpression of vasoconstrictor endothelin 1 and its receptors (14).

Advanced glycation end-products (AGEs) which are thought to contribute to arterial and myocardial stiffness, endothelial dysfunction, and atherosclerosis plaque formation, increases in diabetic patients (7, 8, 15, 16). Extracellular proteins, such as collagen and elastin, are particularly vulnerable to accumulation of AGE crosslink (17). AGEs can easily make covalent cross-linkage with proteins and in this way they change the structure and function of these proteins. Crosslinks in collagen and elastin cause increased myocardial stiffness and impaired cardiac relaxation (4). Also AGEs aggravate intracellular oxidative stress which can contribute to cell damage (15, 16, 18). In addition, hyperglycemia activates local renin-angiotensin-aldosterone system (RAAS), contributing to myocyte necrosis and fibrosis (8, 19, 20). To maintain glucose homeostasis, insulin levels increase compensatory and due to the similarities in the extracellular domains between the insulin receptor and the insulin-like growth factor IGF 1 receptor, increased levels of insulin can promote cellular hypertrophy by binding to the IGF-1 receptor so that insulin acts as growth factor on myocytes (15, 21). Hyperglycemia and hyperinsulinemia stimulate overexpression of transforming growth fac- tor-1 by cardiac fibroblasts, resulting in fibrous tissue deposition and extracellular matrix synthesis (8, 22).

Impaired free fatty acid metabolism

In non-diabetic healthy human, energy required for myocytes come approximately in equivalent proportions from glucose metabolism and free fatty acids (FFA). In diabetic heart due to depletion of glucose transporter proteins, glucose use significantly decreases, myocardial FFA uptake increase and energy production shifts to beta-oxidation of FFA (4, 8, 23). Increased FFA oxidation promotes mitochondrial uncoupling that may result in reduced myocardial high energy reserves and contractile dysfunction (22, 24). FFA’s inhibit pyruvate dehydrogenase and leads to accumulation of glycolytic intermediates and ceramides, which enhance apoptosis (2, 25). In addition, FFA metabolism for adenosine triphosphate production requires large amounts of oxygen that results in more toxic intermediates (lipotoxicity) which impair myocyte calcium handling, worsening myocardial mechanics (8, 15, 23, 26-29).

Microvascular damage and impaired angiogenesis

In diabetics anatomical and functional abnormalities in vascular bed is frequently seen. Major pathological changes are abnormal capillary vasodilatation and permeability, subendothelial matrix deposition and fibrosis surrounding arterioles (8). Hyperglycemia impairs endothelial NO production (by activating protein kinase C), enhances the synthesis of vasoconstrictor prostanoids. Angiogenic response to ischemia is impaired in
patients with diabetes. Hypoxia-inducible factor 1 (HIF-1), a regulator protein that activates the expression of multiple angiogenic growth factors including vascular endothelial growth factor (VEGF). HIF-1 and VEGF levels decreased (40-70%) in the myocardium of diabetic rats (30, 31).

Cardiac autonomic neuropathy
One of the most serious complication of diabetes is cardiac autonomic neuropathy (CAN) which is strongly associated with mortality. CAN is seen in 17% of patients with type 1 diabetes and 22% of those with type 2. CAN basically disturbs the balance of autonomic nervous system that results in loss of heart rate variability and abnormalities in microvascular dynamics (32). Left ventricular (LV) dysfunction is caused by sympathetic denervation (decrease myocardial perfusion and leads to ischemia and necrosis) and changes in myocardial autonomic neurotransmitters levels and beta receptor density (leads to apoptosis and fibrosis) (32, 33).

Disordered copper metabolism
In diabetic individuals serum copper levels increases especially in patients with vascular complications (34). Ceruloplasmin and albumin are the main copper binding proteins in plasma. Hyperglycemia impair the copper binding properties of these proteins and results in increased copper levels in the extracellular matrix (8, 35). Excessive levels of copper in the extracellular matrix is thought to activate the oxidation-reduction process, which leads to increased oxidative stress, apoptosis and fibrosis (36). As a result of this very complicated pathophysiologic process, myocardial structure changes and myocardial performance decrease (8).

Diagnosis
Early determination of myocardial involvement in patients with DM is crucial because development of heart failure worsens the prognosis. Although overt DCP takes years to develop, cardiac abnormalities can be identified with echocardiography or cardiac MRI at the early stages before any HF symptoms exist (25). There are two components in the clinical diagnosis of DCP: the detection of myocardial dysfunction and the exclusion of other co-morbidities that causes similar myocardial abnormalities. Evidence of cardiac hypertrophy (detected by echocardiography or cardiac MRI) or diastolic dysfunction (by transmitral Doppler or tissue Doppler) is essential to support a diagnosis of DCP, but they are not specific for it. The echocardiographic assessment of diastolic functions based on Doppler studies of transmitral velocities, mitral flow patterns and mitral annulus velocities by tissue Doppler imaging. LV relaxation impairs, early diastolic filling decrease, atrial filling deceleration time and isovolumetric relaxation time increases (37, 38).

Systolic dysfunction may develop in subsequent years after these pathological changes (2, 7, 8, 13, 16). It has been showed that, prolonged preejection performance and a shortened ejection period, both of which correlate with reduced resting LV ejection fraction (LVEF) and diminished systolic function in diabetic patients without overt failure (39). Currently we know that diabetic patients have a lower LVEF in response to exercise, suggesting a reduction in cardiac reserve. Also early LV systolic dysfunction with normal LVEF has been described (39). More sensitive techniques for systolic assessment such as strain, strain rate, and myocardial tissue Doppler velocity may detect preclinical systolic abnormalities in diabetic patients (4). In previous studies abnormal transmital inflow velocities were associated with poor glycemic control and returned to more normal profile by improvement of glycemic control, suggested that the process may be reversible in the early stages (8, 40, 41). Ultrasonic backscatter is a new technique that quantifies fibrosis in myocardium based on collagen content. In a previous study of asymptomatic type I diabetic patients without hypertension or CAD and normal systolic function, septal and posterior wall echodensity was significantly higher in diabetics than controls (42). It was suggested that increased myocardial echodensity is related to augmented collagen deposition and this finding may be early marker for the development of the following DCP (37, 42).

Cardiac MRI is gold standard for cardiac dimensions and volume measurements, irrespective of patient body habitus or echocardiographic window. Cardiac MRI provides LV filling parameters which are comparable with echocardiography, in addition to novel morphological (demonstration of fatty or fibrosis infiltrates) and functional parameter assessments, useful diagnostic tools which are not available via echocardiography (8). The more frequent use of MRI has broadened our understanding of DCP and provide the assessing DC in their infancy compared with echocardiography (8, 43, 44).

Also resting electrocardiogram (ECG) may be suggest for underlying DCP in diabetic patients. In our previous study, a poor R-wave progression (defined as an R wave <3 mm in V1-3) in resting ECG of diabetic patients appears to be a promising marker for DCP after eliminating all the other diseases that might cause poor R-wave progression. During follow-up, more patients with poor R-wave progression developed systolic dysfunction compared to patients without poor R-wave progression (19% vs 3%). In addition, LV mass index significantly increased in patients with poor R-wave progression (13).

Prevention and Treatment
Poor glycemic control has been associated with an increased risk of cardiovascular mortality with an increase of 11% for every 1% rise in HbA1c levels (25, 45). Also in previous studies, the degree of diastolic dysfunction was correlated with HbA1c and insulin levels (13, 29, 46, 47). An improvement in metabolic control has been shown to enhance myocardial contractility parameters, which has been explained by more efficient myocardial energy substrate and improved microvascular perfusion (8). It has been suggested that DCP does not develop
in patients with tightly controlled type 1 diabetes, supporting
an important role for hyperglycemia in the pathogenesis of dia-
abetic cardiomyopathy (4). So that strict glycemic control seems
to play the central role for prevention and treatment of DCP
(Table 1).

The rennin-angiotensin-aldosterone system (RAAS) has an
important role in the pathogenesis of complications in diabetic
patients. It has been suggested that an angiotensin receptor
blocker, candesartan improved echocardiographic parameters of
diastolic dysfunction, reduce collagen synthesis, and increase
collagen degradation in asymptomatic diabetic patients (8, 48). RAAS blockers must be kept in mind in all diabetic patients to
reduce cardiovascular mortality.

β-blockade improves ventricular function and patient well-
being, reduces hospital admission for worsening HF, and
increases survival (49). A meta-analysis of the 6 main heart fail-
ure trials, CIBIS-II (Cardiac insufficiency Bisoprolol Study II),
BEST (β-Blocker Evaluation of Survival Trial), ANZ (Australia and
New Zealand) Carvedilol, Carvedilol US Trials, COPERNICUS
(Carvedilol Prospective Randomized Cumulative Survival),
MERIT-HF (Metoprolol Controlled Release Randomized
Intervention Trial in Heart Failure) has subgroup data available
that enables analysis of the diabetic cohort. The pooled relative
risk of mortality in patients with diabetes mellitus and congestive
heart failure on 

blocker treatment compared with placebo was 0.84 (95% CI, 0.73-0.96; p <0.011) (4). As a result β-blockers should be
given to all diabetic patients with any evidence of
heart failure and an LVEF <40%, unless specifically contraindi-
cated or not tolerated.

Today we exactly know that statin therapy reduces cardio-
vascular ischemic events but there was no study, which evalu-
ates the effect of statins on prevention or improvement of DCP.
So, that the efficacy of statins in DCP therefore remains to be
determined.

Although oxidative stress contributes to development of DCP
studies on use of traditional anti-oxidants such as vitamin E or C
has reported disappointed results (50). Novel therapies directed
toward the prevention and progression of DCP, and the majority
of the agents are listed in Table 1 (8). Advanced glycation end-
product inhibitors (eg, aminoguanidine, alanine aminotransfer-
ase 946, and pyridoxamine), advanced glycation end-product
cross-link breakers (eg, alanine aminotransferase 711) and cop-
per chelators (trientine) are some novel experimental agents (6).
Modulators of free fatty acid metabolism such as trimetazidine,
have proven useful in the management of angina, but their effi-
cacy on DCP is unknown.

**Conclusion**

DCP is defined as myocardial structural or functional abnor-
malities in the absence of hypertension, coronary artery and
valvular heart disease. DCP is frequently seen in the asymptom-
atic diabetic patients, screening DCP at the earliest stage of
development is important for long-term prognosis and preven-
tion of the progression to congestive heart failure. The most
frequently used diagnostic methods are standard echocardi-
ogram and cardiac MRI. A less expensive pre-screening method
may be the detection of poor R progression in ECG. Although
strict glycemic control seems to play the central role for preven-
tion and treatment of DCP, we need novel therapeutic agents,
specific to diabetic cardiomyopathy.

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