HIGHLIGHTS IN DIABETIC CARDIOMYOPATHY

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Abstract

Diabetic cardiomyopathy is a clinical condition characterized by altered myocardial function in the absence of coronary artery disease, hypertension, and valvular or congenital heart disease. Patients with this condition exhibit changes in cardiac structure that may be attributed to the direct effect of diabetes mellitus.

Cardiomyopathy in diabetes is associated with a cluster of features including decreased diastolic compliance, interstitial fibrosis and myocyte hypertrophy. The mechanisms leading to diabetic cardiomyopathy remains uncertain. The most important mechanism of diabetic cardiomyopathy is metabolic disturbance (depletion of glucose transporter 4, increased free fatty acids, carnitine deficiency, changes in calcium homeostasis), myocardial fibrosis (association with increases in angiotensin II, IGF-I, and inflammatory cytokines), small vessel disease (microangiopathy, impaired coronary flow reserve, and endothelial dysfunction), cardiac autonomic neuropathy (denervation and alterations in myocardial catecholamine levels), and insulin resistance.

Key words: *diabetes, cardiomyopathy, heart failure, insulin resistance, lipotoxicity*

Introduction

Cardiovascular complications are the main cause of morbidity and mortality in people with diabetes mellitus (DM). DM substantially increases the risk of developing the heart failure (HF) of any etiology, with a severe evolution and worse prognosis than in general population (14). This increased risk is explained by the frequent association with hypertension, present in over 1/3 of diabetic patients, accelerate coronary atherosclerosis and, on the other hand, by the presence of specific changes in the structure and function of the myocardium, defined as diabetic cardiomyopathy (4,12).

Diabetic cardiomyopathy, hypertension and ischemic coronary disease can independently contribute to biochemical, physiological, and anatomical alterations in cardiac tissue, but they often coexist, constituting the "cardiotoxic triad", which causes more severe myocardial dysfunction and increased morbidity by HF in diabetic population (3).

Definition

Diabetic cardiomyopathy refers to a distinct disease entity which affects the myocardium in diabetic patients, independent of hypertension and coronary artery disease (CAD) (12). It is mainly characterized by interstitial fibrosis, alterations in microvasculature, and myocellular hypertrophy, leading to reduction in myocardial compliance and diastolic dysfunction (4,15). With disease progression, salient findings include left ventricular hypertrophy, ranging from asymptomatic diastolic dysfunction to overt systolic HF (8).

Pathology

The pathophysiology of diabetic cardiomyopathy remains largely unknown. We can agree with more mechanisms involved in developing this condition: metabolic disturbances (altered myocardial metabolism, depletion GLUT 4, hyperglycemia, hyperlipidemia, changes in calcium homeostasis); activation of the renin-angiotensin - aldosterone and the sympathetic nervous system (SNS), which contribute to the process of ventricular remodeling and myocardial fibrosis, vascular disturbances (microangiopathy coronary disease, altered coronary reserve flow, endothelial dysfunction), cardiac autonomic neuropathy, insulin resistance (1,8,15).

Hyperglycemia may manifest its damaging effects through a series of secondary transducers. One of the principle abnormalities is the excess generation of advanced glycation end-products (AGEs), which deactivate NO (nitric oxide) and impairs coronary vasodilatation (2). Sustained hyperglycemia causes excess formation of mitochondrial ROS which affects transcription, leading to contractile dysfunction (17). An increase in ROS decreases NO levels, which leads to myocardial inflammation and endothelial dysfunction via PARP [poly (ADP-ribose) polymerase]), inhibition of which has been shown to reverse diabetic endothelial dysfunction (1,15). The severity of diastolic dysfunction correlates with HbA1c levels and the likely cause is AGE-induced formation of ROS, resulting in myocardial collagen deposition and fibrosis. Recently, the process of advanced glycation has been related directly to alterations in myocardial calcium handling and hence contractility (7). SERCA2a (sarcoplasmic/endoplasmic-reticulum Ca^{2+-}ATPase 2a) is responsible for replenishing intracellular calcium stores following release; this results in the termination of contraction thus playing an integral part in cardiac relaxation. SERCA2a is a P-type ATPase that utilizes energy from the hydrolysis of the terminal phosphate bond of ATP to pump calcium against its electrochemical gradient (17). The turnover rate of SERC2a is low, which makes it susceptible to post-translational modification, especially in a chronic condition like diabetes (11). Thus advanced glycation of SERCA2a has been shown to lead to a decrease in its activity and a prolongation of cardiac relaxation (2,15).

Fatty acids. 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. Thus there is increased *β*-

oxidation and mitochondrial accumulation of long-chain acyl carnitines, leading to uncoupling of oxidative phosphorylation (7,17). Enhanced fatty acid oxidation decreases glucose and pyruvate utilization by inhibiting pyruvate dehydrogenase. Pyruvate oxidation is reduced further by pdk4 and activated by PPAR (peroxisome-proliferator-activated receptor) (7,11). The net result is an excess of glycolytic intermediates and increased synthesis of ceramide leading to apoptosis (1). Thus impaired glycolysis, pyruvate oxidation, lactate uptake and a greater dependence on fatty acids as a source of acetyl CoA leads to a perturbation of myocardial bioenergetics and contraction/relaxation coupling (2,12).

Endothelial dysfunction. Endothelial dysfunction is a precursor to and an effect of atherosclerosis. Anatomical and functional abnormalities of the vascular endothelium are commonly associated with diabetes. Both chronic hyperglycemia and dyslipidemia are known to contribute to endothelial dysfunction. Hyperglycemia results in impairment of endothelial cell NO production, increased production of vasoconstrictor prostaglandins, glycated proteins, endothelium adhesion molecules and platelet and vascular growth factors, which cumulatively enhance vasomotor tone and vascular permeability, growth and remodelling (4,17). Endothelial dysfunction also includes the accelerated disappearance of capillary endothelium, weakening of intercellular junctions, altered protein synthesis and altered expression/production of adhesion glycoproteins on endothelial cells promoting attachment of monocytes and leucocytes, as well as their transendothelial migration. Furthermore, hyperglycemia enhances endothelial cell matrix production, which may contribute to basement membrane thickening (11,15). As a result of endothelial dysfunction and increased sensitivity to catecholamine there are repeated episodes of the vasoconstriction with the consequent impairment of myocardial perfusion (8).

RAS (renin–angiotensin system). The activation of stretch receptors in the heart activates RAS and the SNS, leading to changes in myocardial structure and remodeling, which impairs cardiac performance (2). In diabetes an up-regulation of RAS occurs despite minimal changes in myocardial loading. An increased expression of angiotensin II in diabetic rats has been related to cardiomyocyte hypertrophy and apoptosis. IGF-1 (insulin-like growth factor-1) has been shown to down-regulate the binding of p53 DNA, leading to a reduction in the transcription of angiotensinogen and, thereby, angiotensin II, resulting in a reduction in cardiomyocyte apoptosis (11). Similarly over expression of the IGF-1 gene downregulates the RAS system and inhibits the development of diabetic cardiomyopathy (17).

Aldosterone-induced fibrosis. It is known that angiotensin II and aldosterone are able to induce cardiac fibrosis, which is characterized by enhanced accumulation of collagen and increased fibroblast proliferation *in vivo*. *In vitro*, angiotensin II and aldosterone increase the synthesis of collagen by human cardiac fibroblasts in a dose dependent manner (12,15). In addition, angiotensin II also stimulates the proliferation of human cardiac fibroblasts. The existence of a local cardiac renin–angiotensin–aldosterone system comprising all components, including enzymes and receptors, has been demonstrated (8).

Morphopathology

DM induce myocardial structural changes, which can be highlighted necroptic and in vivo with echocardiogram or by microscopic examination of biopsy samples of endomyocardium. Hypertension and CAD often coexist in patients with DM and act synergistically in enhancing cardiac lesions (14).

In the initial stages, diabetic cardiomyopathy is manifested predominantly by morphological alterations at interstitial level, looking relatively normal at macroscopic cardiac echocardiogram examination (4).

In optical microscopy, the changes are characteristic: interstitial fibrosis, hypertrophy, myocitolysis and submission of intracellular vacuole.

Myocardial fibrosis occurs through the accumulation of interstitial glycoproteins and by increasing of extracellular collagen matrix. Myocardial interstitial fibrosis is correlated with the degree of metabolic imbalance. Hyperglycaemia induces the formation and accumulation PFGA . These compounds result from the interaction of glucose with the amino groups (NH2), which causes decreased ability degradation of the substrate protein, by altering the molecular conformation (12).

The glycozilation affects collagen, causing changes in its structure and increasing the number of links and intracellular components, including contractile proteins.

At the extracellular matrix changes occur both qualitative and quantitative. Glycozilation of collagen fibers induces alteration in their organization, with increased links between fibers (15). It notes the significant reduction in the solubility of myocardium collagen, as an indicator of excessive production of links between collagen fibers. In addition increased amount of collagen in myocardium is noted, both by increasing its synthesis, as by reducing degradation of collagen (8).

These changes increase stiffness of the ventricular wall and installation of diastolic left ventricular dysfunction. Chronologically, in the early stages of diabetic cardiomyopathy, the preservation of original morphology maintains a period of time, a normal systolic function (14).

At microvascular level, changes occur typical by thickening of the capillary membrane, intimal proliferation and training capillary microanevrysm, most common in areas of degeneration. Intramural arteriole walls are thick because of fibrosis and accumulation of glycoproteins, PAS positive (12). At the same time, increased permeability of intramural small vessels leads to edema and interstitial fibrosis. Angiogenesis as response to hypoxia, is altered, resulting reduced number of capillary with consecutive ischemic changes.

Macroscopic, diabetic cardiomyopathy is manifested predominantly by left ventricular hypertrophy, with thickening of the interventricular septum and posterior wall of LV.

Hypertrophic cardiomyopathy appears relatively early in the evolution of DM but can regress under intensive insulin therapy and converting enzyme inhibitors.

In advanced stages, especially in conditions of lasting metabolic imbalance, or by association with hypertension and/or CAD occurs a transition from the hypertrophic compensated cardiomyopathy to a decompensate dilatated cardiomyopathy, with the signs and symptoms of HF (14).

At worsening of HF can contribute although papillary muscle fibrosis, which causes mitral valvular insufficiency.

Diagnostic

Echocardiography: clinically apparent diabetic cardiomyopathy may take several years to develop, but echocardiography can detect significant abnormalities well before the onset of symptomatic HF. There are different types of echocardiography which are used in diagnosing LV dysfunction (8,13).

Conventional echocardiography: early abnormalities are defined by a preserved LV ejection fraction with reduced early diastolic filling, prolongation of isovolumetric relaxation and increased atrial filling, the presence of which confirms diastolic dysfunction (15). A reduction in LV distensibility is characterized by an increased pre-ejection period (PEP) and shorter LV ejection time (LVET), resulting in an increased PEP/LVET ratio (4,12,14).

Tissue Doppler echocardiography (TDI): in standard echocardiography, a high-velocity low-amplitude filter looks solely at blood flow through the heart to define valvular function. TDI also quantifies both longitudinal and circumferential cardiac contraction. Longitudinal (long-axis) contraction of the left ventricle is dependent on the integrity of longitudinal subendocardial myocardial fibres, whereas radial (short-axis) contraction depends on integrity of the circumferential fibres (13). The former is more susceptible to ischaemia and fibrosis which may result in a relative increase in short-axis velocity compared with a decrease in long-axis function due to compensatory ventricular remodelling (6,16).

Strong Heart Study showed a direct proportional relationship between the degree of disorder of diastolic reductions LV and microalbuminuria (15). Microalbuminira is a marker of endothelial dysfunction and an independent risk factor for cardiovascular morbidity and development of HF, as proven in HOPE (Heart Outcomes Prevention Evaluation) study (4).

There are three stages of diastolic dysfunction of LV (highlighted by Doppler echocardiography): disturbance of ventricular relaxation, pseudonormal ventricular filling and restrictive filling (8,10).

Diastolic dysfunction is manifested initially by LV relaxation disturbance, characterized in the Doppler examination, by reducing early diastolic filling (assessed by the wave E), extending atrial filling (evidenced by the wave A), a raport E / A <1, the prolongation of izovolumetric relaxation and deceleration time increased (5,10).

Pseudonormal ventricular filling is a pathological phenomenon which can not be differentiated from normal appearance by measuring with Doppler standard, it is required registration of lung flow and appreciation of the transmitral flow after Valsalva maneuver (abnormalities of ventricular relaxation) (12).

Pseudonormal ventricular filling represents a step towards the intermediate stage of restricted filling, which is marked by increase pressure filling of LV, associate with the systolic dysfunction LV, evolving to HF failure and bad prognostic (6,13).

In the evolution of the disease, diastolic dysfunction LV is progressive and associates systolic dysfunction of LV, highlighted by lowering of the EF LV. In addition echocardiography allows examination and identification of morphological changes characteristic diabetic cardiomyopathy as thickening of the interventricular septum and posterior wall (10,14).

In finalizing the diagnosis of diabetic cardiomyopathy, an important role is played by invasive exploration (cardiac catheterism with ventricular function assessment), supplemented with endomyocardic biopsy (15).

Echocardiography should be performed to all asymptomatic patients with diabetes and microalbuminuria.

Staging

There are described 3 stages: from an initial sub clinical phase, with functional changes potentially reversible to structural alterations and irreversible HF.

The early stage of diabetic cardiomyopathy is characterized by metabolic disturbances consecutive to hyperglycemia, such as depletion GLUT 4, increased FFA, carnitine deficiency, changes in calcium homeostasis and insulin resistance, without structural changes in the myocardium and normal systolic and diastolic function (8,13).

However, using more sensitive imaging techniques, such as tissue Doppler echocardiography, which, by detecting intramyocardic velocity allows complex evaluation of LV function; detects diastolic dysfunction in sub clinical stage (15). Endothelial dysfunction is present in the early stage of diabetic cardiomyopathy (4,9).

In the second evolutionary stage, increase disruptions at the cellular level (like deffective transport of calcium, FFA altered metabolism, increased angiotensin II and TGF-β1, reduced IGF-1) induces apoptosis and necrosis, myocardial interstitial fibrosis and cells hypertrophy. These changes increase the stiffness of LV and progressive diastolic dysfunction (detected by conventional echocardiography), the preservation of systolic function at rest, but it is possible EF LV to decrease by effort. At diastolic dysfunction can also contribute autonomic cardiac neuropathy (5,12,14).

Echocardiography may indicate a slight increase in weight of LV and ventricular wall thickness (6,16).

The third stage, advanced, the diabetic cardiomyopathy is characterized by extensive myocardial fibrosis, structural and functional changes of small intramural vessels, left ventricular hypertrophy, sever diastolic dysfunction associated with progressive systolic dysfunction (initial to effort, and at rest later) (9,13).

Prognostic

Diabetic cardiomyopathy is in part responsible for the increased prevalence of HF and reserved prognostic in patients with DM (16). This condition, intricated with coronary disease, contribute to myocardial ischemia symptomatic or asymptomatic episodes and, in association with autonomic cardiac neuropathy, increases the risk of malignant ventricular arrhythmias and sudden death (6,12). The severity of ventricular dysfunction in diabetic patients is correlated with the degree of metabolic control even when there isn't an obvious coronary microangiopathy. This suggests a non-ischemic etiology of the diabetic cardiomyopathy (3,11).

Clinical studies have revealed that diabetic patients have a prevalence of about 3 times higher of HF post myocardial infarction and mortality 2 times higher compared to the nondiabetics. Survival in acute myocardial infarction is related to the area of the coronary lesions, and the myopathy, clinically difficult to quantify, but suggested by retinal and / or kidney microangiopathy (5,9,13).

In the study DIGAMI (Diabetes Insulin Glucose in Acute Miocardial Infarction), 66% of deaths in the first year after a myocardial infarction in patients with DM, were due to HF.

Diabetic patients have a lower survival rate after myocardial revascularization (Percutaneous Transluminal angioplasty, PTCA) or surgical (CABG), compared with those without diabetes mellitus. In the BARI (Bypass Angioplasty Revascularization Investigation) study, at 5-year mortality in diabetic patients with coronary disease was 35% after PTCA and significantly lower, 19% after CABG, showing that people with the DM would prefer surgical myocardial revascularization.

Restenosis after PTCA is higher suggesting that remodeling and neointimal proliferation consecutive angioplasty are emphasized in diabetic patients compared with coronary artery patients without DM (3,8).

Experimental studies have shown that metabolic changes are directly responsible for the contractile dysfunction during ischemia and the injuries of reperfusion after ischemia, aggravating the prognosis (12).

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