REVIEW

Diabetic Cardiomyopathy: Pathophysiology Considerations and Management

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Abstract

Diabetes mellitus (DM) is nowadays considered an epidemic in the industrialized world. Among other complications, it affects the heart and is accompanied by an increased cardiovascular mortality. The development of heart failure (HF) in DM occurs independently of any coronary artery disease or hypertension, and this entity is termed "diabetic cardiomyopathy". Cardiac hypertrophy, abnormal ventricular strain features, diastolic dysfunction and subsequently systolic impairment are the cardinal imaging characteristics. The pathophysiology of the disease is complex and multifactorial and, as a consequence, the therapeutic options, on top of the conventional HF medications, should aim at reversing the pathophysiological processes. Hereby we briefly review the manifestations of diabetic cardiomyopathy, describe the pathogenetic mechanisms and discuss the potential therapeutic targets. ***Rhythmos 2019;14(4):71-76.***

Keywords*:* diabetes mellitus; cardiomyopathy; heart failure

Abbreviations: CAD = coronary artery disease; CV = cardiovascular; DM = diabetes mellitus; HF = heart failure; LVEF = left ventricular ejection fraction

Introduction

Diabetes mellitus (DM) has reached epidemic proportions in the western world. It is associated with increased cardiovascular (CV) mortality independently of the presence of coronary artery disease (CAD).[1-2] CV complications are the main cause of mortality in diabetic individuals [3] and CAD accounts for the majority of the CV deaths and heart failure (HF) cases.[4] The latter are accompanied by poor clinical outcomes, with 5-year survival rates often not exceeding 25%. [5] Interestingly, the incidence of HF among diabetics remains elevated even after adjustment for CAD and hypertension. [6] To describe and characterize this entity, the term "diabetic cardiomyopathy" was proposed,[7] referring to the left ventricular (LV) dysfunction not related to epicardial CAD, valvular abnormalities or hypertension. In this brief overview we summarize the structural features, the pathophysiological considerations and the therapeutic options with regard to this increasingly evolving entity, focusing on type 2 DM, since the available data on type 1 DM are scarce and do not permit definite conclusions.

The heart in diabetes

The first description of the diabetic heart by Rubler et al [7] included myocardial hypertrophy, extensive fibrotic changes and hypertrophy of the myofibrils. Since then, the progress in imaging technology has permitted non-invasive detailed characterization of the cardiac geometry and several studies have demonstrated a variety of structural alterations. An increase of the LV mass has been observed, which may reach 3 g for every 1% rise in HbA1c value. [8,9] The commonest feature is concentric remodeling and it represents a precursor of overt HF. Eccentric remodeling is less common and its relation with CV disease and mortality is less well established.[10,11] In more advanced stages, loss of cardiomyocytes and interstitial fibrosis develops, and its extent has been correlated with the glycemic control. [12-14]

Despite the association between HF and diabetes, most studies have failed to detect reductions in LV ejection fraction (LVEF). One should keep in mind however, that LVEF is an index which lacks sensitivity and is not affected until the late stages of the heart disease. Diastolic dysfunction is a more consistent finding and is thought to represent the early functional change in DM, observed in up to 75% of normotensive, asymptomatic patients. [2,15] The presence of asymptomatic diastolic impairment relates to the subsequent development of overt HF and contributes to mortality.[16,17] Abnormal tissue Doppler parameters have been observed in asymptomatic type 1 (mitral septal and lateral E' velocities, mean ratios E/E'sept, E/E'lat and E/E'total) and type 2 (early velocity-Ea, atrial velocity-Aa, ratio Ea/Aa and systolic velocity-Sa) diabetic patients at an early stage, where conventional echocardiography renders normal results. In the latter population an association with the degree of insulin resistance has been noted. [18,19]

More advanced techniques assessing myocardial strain by tissue Doppler or speckle tracking imaging have shown subclinical systolic dysfunction as well, both in patients with type 1 and 2 DM, children or adults. [20-23] Reduced global longitudinal strain has been more consistently found in diabetics compared to other strain indices and its assessment has been noted to offer additional prognostic value to clinical data, HbA1c and E/E′ ratio. [23]

Pathophysiology concepts

Metabolic adaptation of the heart

Normal cardiomyocytes can use free fatty acids (FFA), glucose, lactate, ketone bodies, and some amino acids, to generate adenosine triphosphate (ATP). The proportional utilization of these substrates is a dynamic process subjected to a complicated integration and depends on substrate availability, oxygen concentration, and myocardial workload. Normally, 90% of ATP is produced in the mitochondria and 60-70% of that from the oxidation of FFA.[24] The regulation of the substrate use is achieved

via the Randle cycle, where fatty acid oxidation (FAO) inhibits glucose uptake, whereas the combination of glucose and insulin inhibits FAO. [25] Free fatty acids enter the cytosolic compartment via transporters, they are esterified to fatty acyl-CoA and depending on myocardial demand, are either stored in the myocardial lipid pool or enter the mitochondria for β-oxidation via the carnitine shuttle. Glucose uptake is mediated by insulin-independent (GLUT1) and insulin-dependent transporters (GLUT4). In diabetes, absolute or relative insulin deficiency increases circulating FFA, which activate peroxisome proliferator activated receptor-a (PPARa), a transcription factor that upregulates myocardial FFA uptake and metabolism. The abundant FFA in the myocardial cytosol is diverted towards the production of diacylglycerol and ceramide which cause myocyte apoptosis. Increased FAO has been shown to be associated with increased myocardial oxygen consumption (MVO2), not accompanied by an equivalent increase in cardiac contractility, which corresponds to reduced cardiac efficiency (cardiac work/MVO2). The process underlying this result is fatty acid-induced impairment of oxidative phosphorylation and uncoupling of ATP synthesis from oxygen consumption. Reactive oxygen species are over produced leading to mitochondrial dysfunction through oxidative stress and further compromise ATP production. This sequence of pathophysiologic events is known as "lipotoxicity" [26,27].

The accumulation of FFA and their oxidation, albeit relatively deficient, inhibits glucose utilization in accordance to the regulation of the Randle cycle. Thus, cardiac glucose oxidation is reduced by 30–40%.[25,28] Elevated cardiomyocyte glucose levels can non-enzymatically glycate proteins to form advanced glycation end-products (AGEs), which enhance reactive oxygen species (ROS) production and can cross-link and damage macromolecules.

The distorted metabolic profile and the compromised mitochondrial function are reflected in the loss of energy balance in the myocardial cell. Diabetic patients have a lower myocardial phosphocreatine (PCr)/ATP than the matched healthy controls, suggesting they are 'cardiac energy-deficient'. [29] This energy deficit has been observed to increase with exercise, indicating impaired cardiac metabolic reserve. [30]

Microangiopathy

Coronary microvascular disease may also account for the cardiac phenotype of DM, at least in part. Epicardial CAD is a well-known complication which is associated with cardiac manifestations in diabetic patients. However, the concept of diabetic cardiomyopathy precludes the presence of significant coronary lesions. Endothelial dysfunction, metabolic derangement of the smooth muscle cells and hormone production and release dysregulation have been proposed to contribute, in combination with oxidative stress and altered cellular signaling, to vasoconstriction and structural remodeling of the coronary vessels.[31,32] Hyperglycemia, hyperlipidemia, and activation of the neurohumoral system may promote alterations in the function and permeability of the endothelium, increased reactivity of the smooth muscle cells and adhesion of inflammatory cells and thrombocytes, to induce vasoconstriction and stimulation of the signaling pathways that result in fibrosis.[32] Microvascular dysfunction has been correlated with albuminuria [33] and the severity of diastolic impairment is proportional to the level of microalbuminuria.[34] These observations suggest a pathogenetic role of micro-angiopathy in diabetic cardiomyopathy.

Advanced Glycation End Products (AGEs)

Persistent hyperglycemia in diabetes causes glycation, a non-enzymatic reaction during which glycose remnants covalently bind to various proteins. These altered molecules exhibit impaired function and with regard to the CV system, are known to cause atherosclerotic plaque formation, endothelial dysfunction, and altered responses to vascular injury. The AGE levels have been correlated with cardiac geometry (LV diastolic diameter) and function (isovolumetric relaxation time).[35,36] However, the effect of tight glycemic control on HF events and diastolic function is not yet clear, since several trials have reported conflicting results. [32,37,38]

Cardiovascular Autonomic Neuropathy

Dysregulation of the autonomic nervous system is known to affect the heart. Sympathetic activation plays a key role in the pathophysiology of HF as increases in β1-adrenergic signaling and expression facilitate interstitial fibrosis, cardiomyocyte hypertrophy and impaired contractile function accompanied by cardiomyocyte apoptosis. [39] Autonomic neuropathy is a common chronic complication of DM, present in 20-65% of patients, depending on the duration of the disease [40] that impairs vascular hemodynamics and heart rhythm. As a consequence, it alters the contractile function of the myocardium and also influences blood flow in the coronary circulation. Both diastolic and systolic dysfunction have been observed in patients with diabetic autonomic neuropathy and the former has been related to the severity of the autonomic imbalance. [41]

Inflammation

DM is widely considered a pro-inflammatory condition. In the presence of insulin resistance,

macrophages and T lymphocytes are activated. Inflammatory cytokines (IL-1β, IL-6, IL-18, TNF-α and TGF-β1) secreted by the M1 macrophages facilitate the development of dilated cardiomyopathy [42] and the secretion of chemokines, growth factors, and proinflammatory cytokines by T helper lymphocytes results in impaired diastolic relaxation and cardiac fibrosis. [43] More sophisticated and complex pathways are also potentially involved, such as the oxidative stress damage via a Ras-related C3 botulinum toxin substrate 1 (RAC1)-mediated activation of NADPH oxidase and endoplasmic reticulum (ER) stress. [44, 45]

Activation of the renin-angiotensin-aldosterone system (RAAS)

In the diabetic heart of animal models, there is an increased density and expression of the angiotensin II receptor. [46] Moreover, intracellular angiotensin II levels are 3.4-fold higher in the myocardial cells of diabetic patients compared with non-diabetics [47] and hence it is supported that hyperglycemia activates the intracardiac RAAS, which promotes the proliferation of cardiac fibroblasts and cardiomyocyte hypertrophy.

Autophagy

Autophagy is a physiological process by which long-lived proteins, ribosomes, lipids and even entire cellular organelles are engulfed by double-membrane structures, which are subsequently targeted to lysosomes for degradation. It is important for the maintenance of normal cellular, protein and organellar function. [48,49] Impairment of this process causes cardiac dysfunction and heart failure. In ischemic injury, during energy depletion, autophagy can be protective, whereas in reperfusion injury it may be detrimental. [50-52] It is currently believed that the degree and duration of autophagy induction determines the benefit or harm produced. [53,54] In diabetic heart models, autophagy has been observed to be activated (type 2 DM) or suppressed (type 1 DM) and the regulatory molecular mechanisms to differ. [55,56] Apparently, this novel concept deserves more focused research in order to be clarified.

Micro RNAs

Micro RNAs are noncoding, single-strand RNAs with an average length of 22 nucleotides, which regulate gene expression by either repressing the translation or by promoting degradation of target mRNAs. They are very popular in basic research lately and diabetic cardiomyopathy makes no exception. Recent reports implicate miR-143, miR-181, miR-103, miR-107 and miR-802 in the pathogenesis of insulin resistance and type 2 diabetes. [57-59] In animal models, miRNA-1 has been linked with cardiomyocyte apoptosis, ventricular dilatation and failure, and miRNA-133 and miRNA-30 regulate connective tissue growth factor expression, suggesting a potential contribution to myocardial fibrosis. [60-61]

The contribution of the type of diabetes

All the previous discussion applies mostly to DM type 2. Type 1 DM is not as thoroughly studied with regard to its cardiac manifestations and their pathophysiological mechanisms. Most of the existing studies show a positive correlation between type 1 DM and HF. [62-65] Each increase of 1% in HbA1c was associated with a 30% higher risk of HF, independently of other risk factors and the risk of HF in patients with type 1 diabetes was similar to that observed in a general population of people that are 15 years older compared to the diabetic cohort. [62] Both systolic and diastolic dysfunction have been established in type 1 diabetic patients, and early systolic impairment as evident by abnormal systolic strain and strain rate values has also been reported. [22,66,67] However, the data on diabetes type 1 are more variable and whether the cardiac dysfunction is attributed exclusively to diabetes has been questioned. Furthermore, one should keep in mind that myocardial injury may be different in type 1 diabetic patients who are usually treated with insulin, which normalizes the metabolic derangements induced by insulin deficiency and underlie the pathophysiology of the heart disease in individuals with type 2 DM. [68]

Therapeutic choices

According to current guidelines, [69] medical therapy in patients with HF is the same regardless of the presence or absence of DM. The use of angiotensin converting enzyme inhibitors (ACEIs) /angiotensin II receptor blockers, beta-blockers, mineralocorticoid receptor antagonists (MRAs) and recently sacubitril/valsartan have been well established in cases with reduced LVEF. Ivabradine, diuretics, the combination of hydralazine and isosorbide dinitrate, and digitalis are also useful, albeit they do not prolong survival. The same agents constitute the fundamentals of management also in heart failure with normal or mid-range ejection fraction, although no mortality benefit has ever been demonstrated.

On the other hand, use of antidiabetic medications in patients with HF is somewhat less liberal compared to patients without CV disease. While metformin was considered contraindicated in HF in the past, data from the last decade have overruled this conception and the drug is included among the first line agents except for cases with severe LV dysfunction. [70,71] Sulfonylureas do not worsen HF, [72] but they are not the preferred option due to the risk of significant hypoglycemia.[32] Thiazolidinediones (peroxisome proliferator activated receptor gamma (γ)

agonists) cause fluid retention and exaggerate HF, as was evident from the RECORD and PROactive trials, [73,74] and are not recommended in patients with HF. Dipeptidyl peptidase IV (DPP-4) inhibitors have shown conflicting results in terms of HF deterioration, [75,76] GLP-1 receptor agonists are rather safe but a more robust confirmation is needed (encouraging results in the LEADER trial, [77] trend towards worse outcome in the FIGHT trial [78]) and sodium-glucose transporter type 2 (SGLT2) inhibitors appear beneficial for HF patients. [79,80]

A more sophisticated approach would be to interfere with the specific pathophysiological pathways of diabetic cardiomyopathy. Modulation of cardiac substrate utilization has been attempted with drugs that reduce plasma-FFA levels (lipoprotein lipase inhibitors), mitochondrial fatty acid uptake (carnitine palmitoyltransferase inhibitors) or fatty acid oxidation (β-oxidation inhibitors). Trimetazidine, an anti-anginal agent with antioxidant potential, is a competitive inhibitor of the terminal enzyme in β-oxidation, which inhibits oxidative phosphorylation and shifts energy production from FFAs to glucose oxidation. [81] It also attenuates the damage caused by free radicals and calcium overload, preserves intracellular ATP and PCr levels, improves endothelial function, and inhibits cellular apoptosis. In animal models it improves myocardial function by augmenting the oxidation status and decreasing lipotoxicity in the heart.[82] In diabetic patients with dilated cardiomyopathy, trimetazidine improved systolic function and physical activity, decreased C reactive protein and NT-pro BNP concentration. [83] Perhexiline, an inhibitor of carnitine 0-palmitoyltransferase 1, increases LVEF, maximal O2 consumption, resting and peak stress myocardial function, and skeletal muscle energetics, [25] but its use is limited due to its potential for peripheral neuropathy and hepatotoxicity. [84]

Another therapeutic target could be mitochondrial oxidative stress and the dysregulation of oxidative phosphorylation. Coenzyme Q10, that acts as an electron carrier in mitochondria and as a coenzyme for mitochondrial enzymes, [85] improves cardiac function in patients with DM and concurrent HF, [86] and it has been shown in a randomized controlled trial of chronic HF patients to be safe, improve symptoms, and reduce all-cause and CV mortality by 42% and 43% respectively. [87] Elamipretide (Szeto-Schiller peptide peptide d-Arg-2′, 6′-dimethyltyrosine-Lys-Phe-NH2 or SS31) is a positively charged free-radical scavenger that can accumulate to high levels in the mitochondria. It can prevent diastolic dysfunction, fibrosis, and cardiac hypertrophy, it maintains the cardiolipin electron-carrying function, protects the structure of mitochondrial cristae and promotes oxidative phosphorylation. [88] Due to these properties, this molecule emerges as a potential option for the reduction of oxidative stress and restoration of normal bioenergetics which are distorted in the diabetic heart.

Finally, genetic therapy may in the future offer a possibility to manipulate the genes that govern the phenotype of diabetic cardiomyopathy. For instance, gene delivery of nerve growth factor preserves microvessel density, cardiac perfusion, and LV diastolic and systolic function, [89] and micro RNA targeted therapy may be of benefit for patients with heart disease and diabetes. However, research is still active on the field and many clinical trials are needed before the theoretical therapeutic possibilities become true applicable options and find their position in the everyday clinical management of diabetic cardiomyopathy.

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