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DIABETIC CARDIOMYOPATHY: PROGRESSION AND PREVENTION

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Abstract

Diabetic cardiomyopathy (DCM) is a complication of disease associated with coronary artery disease (CAD) and myocardial dysfunction in diabetic patients. Various metabolic perturbations are involved in DCM that include depletion of glucose transporter-4 (GLUT-4), increase of free fatty acids (FFAs), microvascular changes and structural and functional changes in myocardium. A number of signaling mechanisms are involved in the pathogenesis of DCM like metabolic disturbances, myocardial fibrosis, small vessel disease, autonomic dysfunction and insulin resistance. In addition, other molecular factors involved in DCM like reactive oxygen species (ROS), nitric oxide (NO), poly(ADP-ribose) polymerase (PARP), protein kiase C (PKC) and advanced glycation end products (AGEs) have been implicated in the pathogenesis of DCM. This review article seeks to evaluate the evidence for the existence of DCM, clarify the potential signaling mechanisms responsible and possible therapeutic implications for the treatment of DCM.

Key words: Diabetic, cardiomyopathy, signaling, complications

Introduction

Cardiovascular diseases have been considered responsible for maximum mortalities among the diabetic patients which are attributed to CAD [1]. However, countless studies show that diabetic patients suffer from an additional cardiac insult referred to as diabetic cardiomyopathy (DCM), which refers to a disease process which affects the myocardium in diabetic patients causing a wide range of structural abnormalities ultimately leading to

LVH (left ventricular hypertrophy) and diastolic and systolic dysfunction or a combination of these [2-3]. The existence of a DCM has been supported by various epidemiological findings alongwith experimental and clinical studies which showed the association of diabetes with heart failure, LV dysfunction, coronary artery disease and other heart diseases [4]. The risk factors associated with the development of DCM include hyperglycemia and hypertension. In addition, various structural and functional features of DCM involve LVH, systolic and diastolic dysfunction [5-6]. The mechanisms of DCM comprise of various metabolic disturbances like depletion of GLUT-4, increased FFAs, carnitine deficiency, changes in calcium homeostasis, myocardial fibrosis, increase in inflammatory cytokines, small vessel disease, cardiac autonomic neuropathy and insulin resistance [7-9]. Moreover, additional molecular factors involved in the pathogenesis of DCM involve ROS, NO, PARP, PKC, AGEs, RAAS (rennin-angiotensin-aldosterone System), KKS (kallikrein-kinin system), HIF-1 (hypoxia-inducible factor-1) and VEGF (vascular endothelial growth factor) [10-11]. Further, a number of agents have been reported in order to treat the patients presented with DCM that involve sulphonylureas, thiazolidinediones, insulin and metabolic modulators [12-14]. This review makes an attempt to provide an evidence of association of these molecular factors in the development and progression of the diabetic heart disease. Moreover, various complications and the strategies to treat DCM have been vitally discussed in the present review.

Risk factors associated with DCM

Many factors can alter and enlarge the pumping chamber of heart, i.e. left ventricle. A number of risk factors recognized in the pathogenesis of DCM have been reported that include hyperglycemia, hypertension, atherosclerosis, heart valve problems, tachycardia, alcoholism, genetic factors, metabolic disorders, nutritional deficiencies of essential vitamins and minerals and neuromuscular disorders [15]. However, hyperglycemia and hypertension have been well reported risk factors associated with DCM. The UKPDS (UK Prospective Diabetes Study) found an increased prevalence of heart failure in Type II diabetic patients, which correlated with higher HbA1c (glycated haemoglobin) levels [16]. Moreover, it has also been reported in the UKPDS that the poor glycemic control was associated with an increased risk of heart failure. Another study showed the correlation of hyperglycemia

with DCM during which improvements in HbA1c and fructosamine levels were demonstrated alongwith improvements in longaxis function (systolic strain rate) and reductions in left ventricular mass (LVM) [10]. In addition, in a 10 year follow-up study of UKPDS, an emergent risk reduction in the mortality associated with myocardial infraction was observed following intensive glucose-lowering therapy [17] (Holman et al., 2008). Further, hypertension has been noted to be independently associated with LVH, diastolic dysfunction, heart failure and cardiovascular risk [13]. This contention is supported by the fact that in the UKPDS, lower BP achieved by a β-blocker or angiotensin converting enzyme (ACE) inhibitor, was associated with a reduced risk of incident heart failure compared with less intensive control of blood pressure [10].

Structural and functional features of DCM

It has been well documented that various structural and functional features are associated with DCM that include LVH and systolic and diastolic dysfunction. LVH has been considered to be a powerful predictor of cardiovascular risk that envisages the prognosis in high-risk patient groups presented with coronary heart disease, heart failure, diabetes, renal failure, hypertension, obesity and myocardial infarction [18-20]. Moreover, studies have also reported an association between diabetes and LVH. The SHS (Strong Heart Study) demonstrated the association between diabetes and higher LVM and wall thickness, increased arterial stiffness and systolic dysfunction, compared with matched controls [21]. Additionally, the MESA (Multi-Ethnic Study of Atherosclerosis) study used cardiac MR (magnetic resonance) to report inter-racial differences in LVM (left ventricular mass), LV volumes and LV function among diabetic patients that further confirmed the association of diabetes with LVH [22]. Another report by the Framingham Heart Study also reported increased LVM across all categories of glucose dysmetabolism. Furthermore, a large population-based study in Sweden demonstrated association between metabolic syndrome, insulin resistance and increased LVM and LV wall thickness [23].

The functional abnormalities are the result of structural remodelling like LVH the outcome of which is the normal or near-normal end diastolic volume, elevated LVM to volume and elevated wall thickness to chamber radius. Certainly, the development of diastolic dysfunction has been associated with only modest increases in LVM [24].

Diastolic dysfunction is characterized by impairment of relaxation and passive filling of the left ventricle. Moreover, the diastolic dysfunction is a common finding in diabetic patients that is thought to be the earliest detectable functional abnormality in DCM [25]. The myocardial collagen deposition, increased cardiomyocyte resting tension and AGEs are the primary pathological processes responsible for reduced elasticity of the myocardium in DCM with reduced LV ejection fraction (LVEF) [26]. LVH and geometric remodelling cause an increase in passive stiffness and impaired relaxation of the ventricles due to which the LV pressure-volume curve gets shifted upward and leftward, chamber compliance gets reduced, diastolic filling is altered with an elevation of the end diastolic pressure, ultimately leading to heart failure (HF). Further, the association of diastolic dysfunction with diabetes is further confirmed by a study of normotensive, asymptomatic Type 2 diabetic patients with good glycaemic control in which 47% were found to have diastolic dysfunction [27]. Another study using more sensitive diagnostic methods has reported that 75% of diabetic patients demonstrate abnormalities of diastolic function [28].

The impairment in the ability of the heart to eject blood is termed as systolic dysfunction, the principle hallmark of which is depressed LVEF. In DCM patients, the systolic dysfunction has been noted to occur late, often when the patients have already developed significant diastolic dysfunction. Moreover, in diabetic patients with HFNEF (HF with a normal EF), long-axis systolic dysfunction has been found to be associated with a compensatory increase in radial thickening and mass [29]. In addition, the patients with HFNEF have significantly higher LVM index (LVMI), lower LVED (left ventricular end-diastole) volume index, higher LVMI/LVED volume index ratio than patients with dilated left ventricles and a low EF, that confirmed the association of systolic dysfunction in DCM [10].

Pathogenesis of DCM

Numerous factors have been found to be involved in the pathogenesis of the functional and structural alterations which lead to the development and progression of DCM. The Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications studies have demonstrated hyperglycemia to be a mediator of cardiovascular risk in Type I and II diabetes [30]. Moreover, hyperglycemia has been noted to induce

oxidative stress which increases profibrogenic factors leading to interstitial fibrosis, a key alteration in DCM. Further, hyperglycaemia promotes formation of collagen types I and III in the myocardium, resulting in interstitial fibrosis, ultimately leading to LV diastolic dysfunction. It has been noted that increased ROS production causes cardiac dysfunction by direct damage to proteins and DNA, as well as by endorsing apoptosis. Moreover, ROS have been well reported to be involved in the development of HF, cardiac hypertrophy and contractile dysfunction [31]. NADPH oxidase enzymes are a source of ROS that are found to be involved in redox signalling by acting as catalysts for electron transfer from NADPH to molecular oxygen, resulting in the generation of free radicals [32]. Moreover, in diabetic animals, the up-regulation of NADPH oxidase correlates with cardiac hypertrophy and up-regulation of pro-fibrotic genes such as pro-collagen III, providing the evidence for the modulatory role of ROS in DCM. Another factor that has been found to be involved in the pathogenesis of DCM is PARP enzymes that are overactivated in diabetes as a reparative response to ROS-induced oxidative damage to DNA [33]. PARP has been noted to inhibit GAPDH (glyceraldehyde-3-phosphate dehydrogenase), which leads to accumulation of glycolytic intermediates that activates a series of transducers which causes tissue damage by AGE formation, NF-κB and PKC activation alongwith overexpression of the vasoconstrictor ET (endothelin)-1 and its receptors [34]. The modulatoy role of PARP in the pathogenesis of DCM has been further confirmed by the fact that hyperglycaemia-induced oxidative stress and up-regulation of extracellular matrix and cardiomyocyte hypertrophy were effectively abolished in PARP-1 knockout mice and in rats treated with the PARP inhibitor ABA (3-aminobenzamide) [35]. PKC activity has been demonstrated to be increased in both failing and diabetic hearts [36]. Moreover, PKC has been noted to phosphorylate a number of proteins directly involved in cardiac excitation-contraction coupling and disturbs calcium handling in cardiomyocytes. A study in transgenic mice overexpressing the PKCβ2 isoform in the myocardium developed cardiac hypertrophy, fibrosis, impairment of LV function and progressive cardiomyopathy that were found to be reversed using a PKCβ isoform-selective inhibitor, evidencing the role of PKC in the pathogenesis of DCM [37]. In addition, the inhibition of PKCα showed significant improvements in cardiac function in rodent models of HF alongwith an improved metabolic gene profile in the myocardium and improved glucose utilization and diastolic function. The

enhanced AGEs formation has been reported to alter structural proteins leading to increased myocardial stiffness that play a supporting role in the pathogenesis of DCM. Aminoguanidine, an inhibitor of AGE formation, ameliorated changes in LV structure and function that further confirmed the modulatory role of AGEs in DCM [38]. Further, it has been well reported that calcium is one of the prime ionic regulators in the heart which is essential for excitation-contraction coupling and normal cardiac function. The cell membrane of the cardiomyocyte gets depolarized and calcium enters the cell through voltage-dependent L-type calcium channels in the sarcolemma during the cardiac action potential. The role of calcium homeostasis in the pathogenesis of DCM has been confirmed by the fact that altered expression, activity and function of all transporters involved in excitation-contraction coupling have been reported in Type I and II rodent models of diabetes [39]. RAAS (rennin-angiotensin-aldosterone system) has been suggested as an important mediator in the pathogenesis and development of DCM. The activation of stretch receptors in the heart has been shown to activate RAS and the SNS (sympathetic nervous system), leading to changes in myocardial structure and remodeling that impairs cardiac performance. Moreover, studies have reported that an upregulation of RAS happen in diabetes in spite of minimal changes in myocardial loading [40]. Further, an increased expression of angiotensin II (Ang-II) in diabetic rats has been related to cardiomyocyte hypertrophy and apoptosis by involving AT1 receptors [41]. In addition, it has been demonstrated that both diabetes and hyperglycaemia induced functional abnormalities in ventricular myocytes, which were prevented by AngII blockade, providing the evidence for their involvement in DCM [42]. Furthermore, an alteration in gene expression has been observed for a number of important inducer and transducer molecules in DCM. Enhanced myocardial gene expression for muscle carnitine palmitoyltransferase 1-8 and additional novel sequences predicted to play a role in signal conduction has been observed after 6 weeks of moderate hyperglycemia in streptozotocin-induced diabetic rats providing the evidence for the involvement of altered gene expression in the development and pathogenesis of DCM [43].

Treatment of DCM

The mechanisms of metabolic disturbances, myocardial fibrosis and microvascular disease associated with DCM imply that various treatments might be effective for preventing or delaying the development of DCM and its

complications. Various treatment strategies include improving diabetic control, use of calcium blockers, angiotensin-converting enzyme (ACE) inhibitors, exercise training, lipid-lowering therapy and antioxidant drugs [5,10]. Hyperglycemia has been well reported to increase the levels of FFA, oxidative stress and growth factors and cause abnormalities in substrate supply and utilization, calcium homeostasis and lipid metabolism. Hence, diabetic control expects to be the most basic and important approach for preventing the development and occurrence of DCM. Another strategy in way of preventing DCM is calcium channel blockade, which is capable of reversing intracellular calcium defects and preventing diabetes-induced myocardial changes. Administration of Verapamil has been shown to significantly improve the depressed rate of contraction and rate of relaxation, lower peak LV systolic pressure and elevate LV diastolic pressure [44]. Further, ACE inhibitors have been noted to facilitate blood flow through the microcirculation in fat and skeletal muscles. Captopril has been demonstrated to increase the number of perfused capillaries and epicardial perfusion rate in order to prevent the increase of coronary perfusion pressure and end-diastolic pressure in diabetic rats [45]. In addition, Ang II receptor blockers and aldosterone inhibitors show similar effects on myocardial fibrosis in diabetic patients. Further, exercise has been reported to improve glucose homeostasis by reducing the glucose/insulin ratio and increasing insulin sensitivity. Studies have shown that exercise training increases whole body insulin sensitivity and glucose oxidation by skeletal and cardiac muscle. Exercise training has also been noted to improve cardiac output and reverse the changes in contractile properties of the heart in streptozotocin-diabetic rats [46]. The role of antioxidants in the prevention and treatment of DCM has been supported by the fact that chronic vitamin E, acetyl-l-carnitine and lipoic acid administration improved the ratio of cardiac sympathetic to parasympathetic tone in patients with type II diabetes, which might be attributed to their potential to reduce oxidative stress [47]. Moreover, aldose reductase inhibitors have demonstrated clinical improvement of cardiac performance in the patients presented with DCM. Chronic stimulation of the sympathetic nervous system leads to increased heart rate and altered gene expression leading to cardiac remodeling diabetes. Beta (β)-blockers have been noted to prevent and reverse cardiac remodelling, resulting in improved LV function and a reduction in mortality in DCM patients [13,48]. Additionally, the hydroxymethylglutaryl CoA reductase inhibitors, commonly

known as statins have shown beneficial outcome in the prevention and treatment of DCM that may be attributed to their pleitropic effects. Numerous studies have shown statins to reduce vascular event rate and improve LV dysfunction in diabetic patients [10,49].

Conclusion

In this review, we presented various risk factors associated with the development and progression of DCM. Moreover, various factors involved in the pathogenesis of DCM have been discussed that include ROS, NO, PARP, PKC and AGEs. In addition, prominent functional consequences include diastolic and systolic dysfunction. At present, none of the specific therapeutic strategies can be recommended for DCM due to unavailability of any comprehensive therapy, but management of traditional risk factors and lifestyle modification should be followed. Further research is needed in order to completely study about the pathogenetic, diagnostic and therapeutic basis of DCM in order to provide more appropriate therapies for the prevention and treatment of DCM.

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