ejpmr, 2016,3(3), 120-128

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 3294-3211

EJPMR

DIABETIC CARDIOMYOPATHY: A REVIEW

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Article Received on 03/01/2016 **Article Revised on 23/01/2016** **Article Accepted on 13/02/2016**

ABSTRACT

Diabetes is recognized as a prevalent risk factor for cardiovascular morbidity and mortality. The core metabolic defects that mark diabetes, including impaired glucose tolerance, insulin resistance and proinflammatory state leading to endothelial dysfunction forms the pathogenesis of diabetic cardiomyopathy. Hyperglycemia triggers series of maladaptive stimuli that result in myocardial fibrosis and collagen deposition. Hyperglycemia induced mitochondrial reactive oxygen species (ROS) is also a significant contributor. Moreover, increases in sympathetic tone with diabetes are associated with changes in cardiac and vascular functions. ANS is responsible for modulating the activity of the sinus node (heart rate), ventricular (end systolic and diastolic volume) and blood vessels (systemic vascular resistance) and the dysfunction of the ANS may contribute to the development of arterial stiffness, left ventricular hypertrophy and ventricular diastolic dysfunction and cardiac autonomic neuropathy; such changes forms the symptoms for cardiomyopathy. Echocardiography is the preferred diagnostic approach for diabetic cardiomyopathy. Magnetic resonance imaging and spectroscopy along with contrast agents are now leading approaches in the diagnosis of myocardial fibrosis, cardiac and metabolic changes. Also, serum biomarkers offer clear picture of diabetes induced structural and functional changes in cardiac even at very early stages of the disease. Currently, there is no specific treatment for diabetic cardiomyopathy. The pillars in the treatment of diabetic cardiomyopathy include lifestyle changes, intense glycemic control through diet, oral hypoglycemics and insulin, modification of risk factors for cardiovascular disease, and management of heart failure symptoms. Although glycemic control is the main therapeutic approach, newer treatment targets are currently being explored.

KEYWORDS: Diabetic cardiomyopathy (DCM), diabetes, cardiovascular disease, myocardial fibrosis, left ventricular hypertrophy.

INTRODUCTION

Diabetic cardiomyopathy (DCM) is defined as the disease process which affects the myocardium in diabetic patients causing myocardial dilatation and hypertrophy, as well as a decrease in the systolic and diastolic function of the left ventricle. Its presence is independent of the coexistence of other confounding factors such as coronary artery disease (CAD), ischemic heart disease or hypertension. DCM may be subclinical for a long time, before the appearance of clinical symptoms or signs.[1] According to the molecular theory of DCM, hyperglycemia is the main pathogenetic factor, which triggers a series of maladaptive stimuli that result in myocardial fibrosis, abnormalities at the cardiac myocyte level and collagen deposition. Hyperglycemia induced mitochondrial reactive oxygen species (ROS) is also a significant contributor, eventually leading to structural and functional abnormalities.[2]

Clinical manifestations of diabetic cardiomyopathy

- **Left Ventricular Hypertrophy**

Diabetes is an independent contributor to left ventricular hypertrophy (LVH) and myocardial stiffness. Patients with diabetes show significant increase in left ventricular mass as compared to patients with impaired or normal fasting blood glucose level[3], suggesting that structural alterations of the heart in diabetic individuals are not an early defect but, rather, a consequence of changes associated with diabetes such as hyperglycemia or obesity. Retinopathy and nephropathy associated with type-1 diabetes, can also affect myocardial remodeling.[4]

- **Diastolic dysfunction**

Diastolic dysfunction is one of the main characteristic of DCM. It is indicated by reduced early diastolic filling, increased atrial filling, extended isovolumetric relaxation and increased supraventricular premature beat.[5] Diastolic dysfunction may precede the development of systolic dysfunction. Indices for diastolic dysfunction such as E/E' and E/A' ratios (where E is the flow related to early ventricular filling and E' and A' are early and

late diastolic velocities, respectively) are also impaired in diabetic patients.[6,7]

- **Systolic dysfunction**

Systolic dysfunction is impairment in the ability of the heart to eject blood.[8] Systolic dysfunction occurs often when patients have already developed significant diastolic dysfunction. In a population of diabetic patients with several degrees of complications, systolic dysfunction was observed in 39% of those with complications and in only 6% of those free from complications.[9] In addition, a subtle systolic dysfunction, which is usually characterized by a low left ventricular ejection fraction (LVEF), is also seen.[10]

- **Interstitial fibrosis**

Interstitial fibrosis, perivascular fibrosis and collagen deposition are primary structural changes of diabetic cardiomyopathy. Diabetes activates myocardial renin angiotensin and endothelin systems which eventually lead to myocyte necrosis and fibrosis.[11] Type I and III of collagen mainly deposits in the epicardial and perivascular regions, whereas type IV predominates in the endocardium.[12]

- **Increased cell death and oxidative stress**

Diabetic myocardium is susceptible to higher myocyte cell death by apoptosis and necrosis. Studies suggest that hyperglycemia results in production of reactive oxygen species, contributing to accelerated apoptosis. Apoptosis was maximally induced in the diabetic myocardium, whereas hypertension exaggerated the process of necrosis.[13,14] Although, majority of reactive oxygen species (ROS) are generated in the mitochondria, enzymatic systems capable of generating ROS in the cytosol such as NADPH oxidase can be modulated by hyperglycemia.[15]

- **Myocardial lipotoxicity**

Diabetic cardiomyopathy is also characterized by increased deposition of lipids in myocardium, which can contribute to cell death and cardiac dysfunction. There is significant increase in myocardial triglyceride and cholesterol that is exacerbated by diabetes. Increased myocardial triglyceride in diabetic patients was associated with diastolic, but not systolic, dysfunction.[16]

Stages of diabetic cardiomyopathy

Based on the clinical phenotypes, Maisch *et al.*[17] have proposed the following classification of diabetic cardiomyopathy.

- **Stage 1**

Diabetic patients are often associated with hypertrophy without relevant hypertension and has normal ejection fraction. It is the earliest form of diabetic cardiomyopathy and can be detected in 75% of asymptomatic diabetic patients.[18]

- **Stage 2**

Systolic and diastolic dysfunction with dilatation and normal or slightly decreased ejection fraction. Myocardial infarction or uncontrolled hypertension should not be present.

- **Stage 3**

Systolic and/or diastolic heart failure in diabetic patients with microvascular disease. Reduced ejection fraction. Hypertension, micro angiopathy and viral heart disease with or without myocarditis can be the contributing factors.

- **Stage 4**

Heart failure attributed to infarction or ischemia and remodelling in addition to stage 3, leads to heart failure in diabetes or stage 4-diabetic cardiomyopathy.[17]

Molecular mechanisms

Diabetes mellitus is a complex disease characterized by hyperglycemia as a result of insulin deficiency or in many instance, it is associated with insulin resistance. The whole pathophysiology of diabetic cardiomyopathy centres around diabetes mellitus, as it serve as a key factor eliciting changes at the molecular and cellular levels of the myocyte, resulting in structural and functional abnormalities in the heart.[19]

- **Hyperglycaemia**

Hyperglycemia plays a central role in the pathogenesis of diabetic cardiomyopathy. Cardiac injury due to chronic hyperglycemia results from the direct and indirect effects of glucose on cardiomyocytes, cardiac fibroblasts, and endothelial cells. Chronic hyperglycemia stimulate the overproduction of reactive oxygen species (ROS) inducing apoptosis and activates poly (ADP-ribose) polymerase-1 (PARP) enzyme that mediates direct ribosylation and inhibition of glyceraldehyde phosphate dehydrogenase (GAPDH) and diverts glucose from the glycolytic pathway toward alternative biochemical series such as increases in advanced glycation end products (AGEs) and the activation of the hexosamine pathway, the polyol pathway, and protein kinase C that eventually lead to hyperglycemia-induced cellular injury.[20,21] Apoptosis induced by hyperglycemia is stimulated by ROS, PARP, AGEs and aldose reductase.[22-25] Cardiac structural and functional changes are the result of post translational modification of extracellular matrix components such as collagens and altered expression and function of sarcoendoplasmic reticulum calcium ATPase (SERCA), which contribute to decreased systolic and diastolic function.[20]

- **Hyperlipidemia**

Enhanced lipogenesis in hepatocytes and increased lipolysis in adipocytes, together lead to increase in circulating fatty acids and triglycerides in patients with diabetes. Insulin resistance and calcium transporter protein dysfunction also elevate the level of free fatty acids (FFAs) which eventually lead to impaired cardiac function. Increased fatty acids are also associated with the activation of proliferation activated receptor-α (PPARα), that promote mitochondrial uncoupling of oxidative phosphorylation, causing depletion myocardial high energy reserves and contractile dysfunction.[26,27] Increased intracellular FFAs may also lead to cardiomyocyte damage and death by apoptosis when

ROS generation exceeds degradation, leading to ROS accumulation (oxidative stress).[28]

- **Mitochondrial dysfunction and oxidative stress**

Hyperglycemia promotes production of mitochondria derived ROS and Rac1mediated increases in NADPH[29], each promoting accelerated apoptosis causing myocardial remodeling and dysfunction. In addition, increased ROS generation due to high FA oxidation induces pathological accumulation of ROS and consequent oxidative stress and cell damage.[30,31] A recent report suggests that the transcription factor p53 which is induced by ischemia, chronic pressure overload, or metabolic disturbances contributes to cardiac dysfunction in diabetes by promoting mitochondrial oxygen consumption, ROS production, and lipid accumulation.[32]

- **Abnormalities in intracellular Ca^{2+} homeostasis**

Ca^{2+} enters the myocardial cells through L type calcium channels, during each heartbeat. This result in increase in intracellular Ca^{2+} which further triggers Ca^{2+} release from the sarcoplasmic reticulum (SR), raising Ca^{2+} levels around the sarcomere. Binding of Ca^{2+} to troponin C initiates actin-myosin cross-bridging causing myocardial contraction. Ca^{2+} reuptake into the SR by SERCA (sarcoendoplasmic reticulum calcium ATPase) and consequent declines in cytoplasmic Ca^{2+} results in cardiac relaxation. Oxidative stress, accumulation of long chain acetyl carnitines and abnormal membrane lipid content contribute to the alteration in the expression of the SERCA and cause abnormalities of Ca^{2+} handling resulting in decline of cardiac function in diabetic cardiomyopathy.[30]

- **Poly (ADP-ribose) polymerase (PARP)**

PARP enzymes are over activated in diabetes as a reparative response to ROS-induced oxidative damage to DNA. PARP inhibits GAPDH (glyceraldehyde-3-phosphate dehydrogenase), which leads to accumulation of glucose and other glycolytic intermediates, which in turn activate tissue damage via polyol pathway, advanced glycosylation end-product formation and PKC (protein kinase C) activation. PARP also promotes cardiac damage by activating NF-κB (nuclear factor κB)[33] and inducing over expression of the vasoconstrictor ET (endothelin)-1 and its receptors causing hypertrophy and fibrosis.[34]

- **Advanced glycosylation end-products (AGEs)**

Hyperglycaemia promotes formation of collagen types I and III in the myocardium, resulting in interstitial fibrosis, which leads to LV diastolic dysfunction; however, the mechanism is unclear. It may alter structural proteins and lead to increased myocardial stiffness.[35]Also, oxidative stress increases expression of AGE and RAGE (receptor for AGEs) leading to an activation of NF-κB which leads to a change of gene expression of cardiac MHC (myosin heavy chain) from the α-MHC isoform to the β-MHC isoform altering myocardial contractility and ultrastructure in left ventricular myocardium.[36]

- **High-mobility group protein B1 (HMGB1)**

HMGB1- high mobility group box-1 protein initiates a robust signal for host defence in response to cell injury or death. HMGB1 plays a major role in diabetes mellitus and remodeling by the activation of sustained pro-inflammatory pathways and enhanced myocardial injury. Volz HC *et. al* in a study exposed mouse cardiomyocytes to elevated glucose which led to a sustained induction of HMGB1 and increased binding to RAGE; followed by increased NF-κB binding activity and sustained increases in TNF-alpha and IL-6 expression.[37]

- **Protein Kinase C (PKC)**

PKC activity is increased in diabetic hearts and its level is correlated with ROS and PARP activity.[38] PKC leads to phosphorylation of a number of proteins that are directly participate in excitation–contraction coupling mechanism of heart, thereby disturbing calcium level in cardiomyocytes.[39] Certain studies showed that over expression of the PKCβ2 isoform found in the myocardium is responsible for development of cardiac hypertrophy, fibrosis, left ventricular.[40] Elevated glucose level tends to increase the activation of the DAG (diacylglycerol)-activated PKC signal transduction pathway in vascular tissues of diabetic patients, inducing many changes in diabetic cardiomyopathy which include a reduction in tissue blood flow, enhanced extracellular matrix deposition, capillary basement membrane thickening and increased vascular permeability.[41]

- **Hypoxia-Inducible Factor-1**

HIF-1 is a transcriptional regulator complex that operates through a hypoxia response element (HRE) present in many gene promoters, including vascular endothelial growth factor (VEGF).[42] It controls the expression of multiple angiogenic growth factors, including angiopoietin-1, 2 and 4, placental growth factor, platelet-derived growth factor-β and VEGF.[43,44] and brings about angiogenesis in chronic cardiac ischemia. In diabetic patients, this angiogenic response to myocardial ischemia is significantly reduced mainly due to reduction of VEGF and its receptors VEGF-R1 and VEGF-R2 (40–70%) in the myocardium, with a 2-fold reduction in VEGF and VEGF-R2 in ventricles from diabetic patients compared with non-diabetics.[42]

- **RAS (renin–angiotensin system)**

Up-regulation of the RAS in diabetes is associated with development of cardiac hypertrophy and fibrosis. Cardiomyocytes and endothelial cells of diabetic hearts manifest evidence of oxidative stress, apoptosis and necrosis that correlate with RAS activation.[45,46] Angiotensin II (Ang II) also has direct effects on cardiomyocytes and cardiac fibroblasts through AT1 receptors, promoting cardiac hypertrophy and fibrosis, characterized by enhanced accumulation of collagen and

increased fibroblast proliferation.[47] Apart from action on cardiac[48], Ang II also have effect on the insulin receptor (IR), IRS proteins found in insulin-sensitive tissues, such as liver, skeletal muscle and adipose tissue bringing upon the phosphorylation of both the IR and IRS-1 proteins leading to desensitization of insulin action.[49]

- **Endothelial Dysfunction and arterial stiffness**

Both chronic hyperglycaemia and dyslipidemia are known to contribute to endothelial dysfunction resulting in impairment of endothelial cell nitrous oxide (NO) production, increased production of vasoconstrictor prostaglandins, glycated proteins, endothelium adhesion molecules and vascular growth factors, which together enhance vascular permeability, growth and remodelling.[50] Endothelial dysfunction lead to increased arterial stiffness in diabetes leading to an increase in central systolic pressure and LV after load which eventually may lead to myocardial ischemia, interstitial fibrosis and heart failure.[51]

- **Autonomic Neuropathy**

Diabetic autonomic neuropathy can lead to changes in sympathetic innervations and altered adrenergic receptor expression and catecholamine levels in the myocardium. Moreover, increases in sympathetic tone with diabetes are associated with enhanced apoptosis, fibrosis and changes in cardiac functions. Dysfunction of the ANS may further contribute to the development of arterial stiffness, left ventricular hypertrophy and ventricular diastolic dysfunction and cardiac autonomic neuropathy.[52,53]

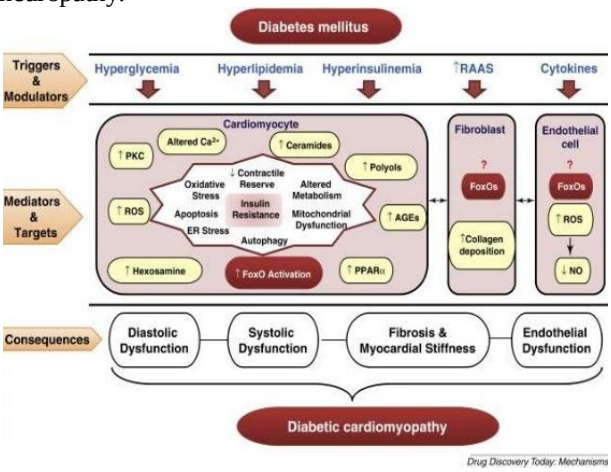

Fig. 1: Pathophysiology of diabetic cardiomyopathy.

Diagnostic methods

Currently used diagnostic methods in clinical practice include echocardiography, cardiac MRI and cardiac biomarkers such as NT-BNP [N-terminal pro-BNP (brain natriuretic peptide)].

Echocardiography

Echocardiography is an inexpensive tool that allows clinicians to evaluate changes in heart structure/function. LVEF (left ventricular ejection fraction) is the most commonly used index of LV systolic function can be derived echocardiographically. Quantitative and qualitative assessment of the heart can be made with regard to LV (left ventricular) geometry, regional wall motion and systolic and diastolic function, in addition to valvular anatomy and function. The main limitation of two-dimensional echocardiography is for patients with major distortions of LV geometry.[54,55] Pulsed-wave Doppler echocardiography, also known as transmitral Doppler (TD), is therefore the most practical and commonly used technique used to assess diastolic function in the heart. Alterations in blood flow velocities due to myocardial fibrosis, hypertrophy, contractile asynchrony, cellular disarray, changes in calcium cycling and pericardial abnormalities, are observed by Doppler.[56]

Cardiac MRI (magnetic resonance imaging)

Cardiac MRI, owing to its superior accuracy and reproducibility, is the 'gold standard' for measuring LV mass and allows the accurate determination of cardiac structure/function.[57] Cardiac magnetic resonance (CMR) affords safe and accurate myocardial measurement and measurement of chamber size, ejection fraction and myocardial mass due to its high contrast and spatial resolution, low noise, and multimodal capability. Cardiac MR is usually sort into black-blood imaging and bright-blood imaging. In the case of black-blood imaging, the produces fine quality images of the cardiac chambers and vessels.[58,59] Bright-blood imaging uses steady state free precession to acquire myocardial function information. Currently however, its use is mainly limited to research, due to costs, time constraints and the expertise required for assessment.[60]

Cardiac biomarkers

Serum aminoterminal propeptide of type I (PINP) and type III (PIIINP) respectively are the indicators of type I and III collagen synthesis.[61] Quilliot *et al.* demonstrated increase of PIIINP in obese subjects with insulin resistance and suggested that this may serve as a biomarker of left ventricular dysfunction.[62] Ihm *et al.* correlated the increase of carboxyterminal telopeptide of type I collagen (ICTP), an indicator of type I collagen degradation, with cardiac remodeling[63] and LV diastolic function. B-natriuretic peptide (BNP), a cardiac neurohormone is predominantly released from myocardium in response to LV volume expansion and pressure overload. BNP levels are elevated in patients with LV dysfunction and correlate to New York Heart Association class and prognosis.[64] These results support the concept that the combined used of biomarker assays and imaging techniques may provide valuable information about diabetes induced changes in cardiac structure/function.

Treatment

Glycemic control

Good glycemic control is beneficial in the early stages of myocardial dysfunction. Evidence suggests that diabetic cardiomyopathy does not develop in patients with tightly

controlled type 1 diabetes. Hyperglycemia contribute significantly to the pathogenesis of diabetic cardiomyopathy, therefore, good glycemic control is perhaps the most important component in the overall management of diabetic cardiomyopathy.[65]

Neurohormonal Antagonism

Treatment with angiotensin converting enzyme inhibitors (ACE inhibitors) has been shown to exert an ameliorative effect on diabetic cardiomyopathy. Evidence suggests that myocardial fibrosis, cardiac hypertrophy and myocardial dysfunction associated with diabetic cardiomyopathy can be prevented by ACE inhibitors. ACE inhibitors and angiotensin-1 receptor blocking agents have also been shown to prevent coronary perivascular fibrosis, collagen deposition and cardiac hypertrophy.[66,67] Evidence also suggests that aldosterone antagonism has beneficial effect in diastolic heart failure.[68,69] Administration of ramipril (2.5 mg/day) for 3 months to type 2 DM patients with early diabetic cardiomyopathy has improved LV diastolic function.

Cross Link Breakers

Collagens type I and III form a basis for maintaining the physical structure of the heart as well as cardiovascular function. AGEs are also formed increasingly in diabetes. Limited human data indicate that cross-link breakers can offer benefit in diabetic cardiomyopathy as they caused a significant reduction (approximately 40%) in left ventricular stiffness, which was accompanied by improvement in cardiac function.[70] Another study demonstrated that cross-link breakers can restore LV ejection fraction, reduce aortic stiffness and LV mass and reverse the up regulation of collagen type I and type III.[71] Alanine aminotransferase 711, an advance glycation end product cross-link breaker is used as a potential tool in the therapy of cardiovascular damage related to diabetes.

Poly (ADP-ribose) polymerase (PARP) inhibitors

Poly (ADP-ribose) polymerase (PARP) contribute significantly to the pathogenesis of diabetic cardiomyopathy thus, PARP inhibitors provides a excellent approach to treat diabetic cardiomyopathy as it blocks activation of all the major pathways thought to mediate cardiac damage in diabetes.[72] These agents reduces diabetic cardiovascular complications, myocardial hypertrophy, atherosclerosis, vascular remodeling. Certain studies conducted by Pacher *et al.* demonstrated that PARP inhibitors PJ-34 or INO-1001 attenuated the development of cardiac dysfunction, myocardial nitrotyrosine formation and increased the survival in doxorubicin-induced mouse cardiomyopathy models.[73]

Statins (hydroxymethylglutaryl CoA reductase inhibitors)

In addition to the direct effect on cholesterol metabolism, they may have a range of additional benefits, including enhancing endothelial cell nitric oxide synthase activity, preventing AGE induced NF-κB (nuclear factor κB)-induced protein-1 activation and preventing the up-regulation of VEGF mRNA.[74] The landmark 4S (Scandinavian Simvastatin Survival Study) demonstrated a significant reduction of relative risk of major cardiovascular events in patients who have metabolic syndrome.[75,76] Statin therapy is associated with decreased mortality among patients with left ventricular dysfunction.

Thiazolidinediones (TZDs)

The TZDs are insulin sensitizing agents that have agonistic action PPARγ (peroxisome-proliferator-activated receptor γ) receptor. Apart from anti-hyperglycaemic action, these drugs also exert beneficial effects on the myocardium and vascular endothelium.[77] Certain experimental studies have demonstrated that TZDs reduces cardiac hypertrophy and improved systolic and diastolic function. TZDs such as rosiglitazone and pioglitazone increase the expression and function of glucose transporters in the heart, leading to improved glucose metabolism and protect against myocardial injury.[78]

β-Blockers

β-blockers have been shown to prevent and even reverse cardiac remodelling, resulting in improved LV function and a reduction in mortality. Chronic treatment with metoprolol has been shown to improve cardiac function. Carvedilol, a third generation β blocker which antagonizes both α and β receptors, has been shown to have a highly significant effect on both morbidity and mortality (67% reduction).[79]

New therapeutic directions

- Some new therapies directed toward prevention and treatment of diabetic cardiomyopathy targeting hypertrophy, diastolic and systolic dysfunction, enhanced fibrosis and collagen deposition or other alterations in cardiomyocytes, are still in experimental stages. AGEs inhibitors like aminoguanidine, alanine aminotransferase 946, and pyridoxamine, copper chelation therapy (e.g. trientine) and modulators of free fatty acid metabolism (e.g. trimetazidine), agents like exenatide (recombinant glucagon-like peptide-1) or sitagliptin (DPP4 inhibitor) are studied specifically in patients with diabetic cardiomyopathy despite promising cardiac effects.[80]
- Mitochondrial oxidative stress and mitochondrion dependent myocardial apoptosis can be suppressed with the administration of antioxidant α-lipoic acid (α-LA) and prevent evolution of DCM due to increase in the activity of manganese superoxide dismutase in the myocardial mitochondria and an increase in the glutathione content of myocardial mitochondria.[81]
- In a study, breviscapine targeted the β-isoform of protein kinase C (PKC-β) that forms one of the

causes of DCM. Treatment with breviscapine reversed the cardiac dysfunction and structure changes in rats with DCM, decreased the expression of PKC.[82,83] Also, treatment with PKC-β inhibitor, ruboxistaurin for 6 weeks reduced cardiomyocyte hypertrophy, diastolic dysfunction and collagen deposition in diabetic animals.[84]

- LY333531, a PKC*β* isoform-specific inhibitor, has been shown to be efficacious in a number of phase II clinical trials in diabetic retinopathy, nephropathy, neuropathy and cardiac dysfunction. Phase III clinical trials are currently underway for a number of indications, including diabetic cardiomyopathy.[85]
- An experimental study showed that 4-week administration daily vivo administration of sodium selenate or pure ω-3 fish oil with antioxidant vitamin E (ω-3E) prevented the diabetes induced cardiac functional changes and could have therapeutic benefits in DCM.[86]
- Recent studies have demonstrated that kinins, which are vasoactive peptides and part of the kallikrein–kinin system (KKS), are involved in cardiac remodeling, inflammation and angiogenesis. Evidence shows that the KKS protects the myocardium from inflammation, fibrosis, and apoptosis. KKS contribute to neovascularisation and recruitment of endothelial progenitor cells in ischemic areas and endothelial dysfunction therefore; KKS can serve as a potential therapeutic target in the treatment of DCM.[87]
- Reduction of the sarcoplasmic calcium ATPase myocardial expression (SERCA2) plays a significant role in the myocardial dysfunction of DCM. Certain data demonstrate that Resveratrol, a potent activator of the cardiac function enhances the expression of the SERCA2 and improves cardiac function.[88]
- Also, HMGB1 plays a major role in diabetes and remodeling by binding to RAGE, resulting in activation of sustained pro-inflammatory pathways and enhanced myocardial injury. Therefore, blockage of HMGB1 might represent a therapeutic strategy to reduce post-ischemic remodeling in diabetic patients.[37]

Herbal approaches

- Studies have shown that two phenolic acids naturally occurring in many plant foods, caffeic and ellagic acid have antioxidative, triglyceride-lowering and anti-inflammatory properties and can protect cardiac tissue in diabetic mice. Thus these agents might be helpful for the prevention of DCM.[89]
- Grape seed proanthocyanidin extracts (GSPEs) can also serve as therapeutic agents against DCM in streptozotocin-induced diabetic rats. GSPEs decreased AGEs and ameliorated glycation-associated cardiac damage.[90]
- In a study, the effects of *Ginkgo biloba* extract (EGb 761), a radical scavenger, was evaluated against diabetes-induced myocardial interstitium and microvasculature damage in experimental rats. Pretreatment of diabetic myocardium with EGb preserved myocardial ultrastructure and functions compared with unprotected myocardium, suggesting that EGb may act as a potent therapeutic adjuvant in preventing late complications in DCM.[91]
- A recent study demonstrated that total aralosides of *Aralia elata* (Miq) Seem (TASAES) derived from the Chinese traditional herb Longya *Aralia chinensis* L. has been found to improve cardiac function in DCM in streptozotocin-induced diabetic rats. Treatment with TASAES for 8 weeks prevented diabetes-induced cardiac dysfunction and pathological damage.[92]

CONCLUSION

Diabetic patients are prone to significant changes at the cellular level causing functional and structural abnormalities in the myocardium, leading to diabetic cardiomyopathy. Cause is likely multi-factorial but clearly related to hyperglycemia, enhance FFA utilization, oxidative stress, renin-angiotensin system up regulation and mitochondrial dysfunction that eventually contributes to the development of arterial stiffness, left ventricular hypertrophy and ventricular diastolic dysfunction. Poly (ADP-ribose) polymerase (PARP), advanced glycosylation end-products (AGEs), dysfunction of the ANS, high-mobility group protein B1 (HMGB1) also promotes cardiac damage and remodelling. Echocardiography currently stands as the preferred diagnostic approach. With the advent of cardiac MR, myocardial fibrosis has been easier to detect. Although there are no specific therapies, careful glycemic control and early administration of neurohormonal antagonists currently remains the mainstay of therapy. Many newer treatment targets are being explored showing promising initial results, however, further trials are needed for proven benefits. Future considerations involve earlier and more precise diagnosis, identification of the culprit pathophysiology and elucidation of new treatment targets, e.g. HMGB1.

ACKNOWLEDGEMENT

Authors are thankful to Professor H.H. Siddiqui for their generous guidance and Professor S. W. Akhtar, hon'able Vice Chancellor, Integral University, for providing of all the necessary facilities for this work.

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