Abstract

Diabetes is associated with most of the risk factors associated to the vital organs like Heart, Kidney, Liver and Brain. Although there is no much evidence to understand the clear mechanism of the Diabetic Cardiomyopathy to have increased Heart Risk, it becomes very important to understand the possibilities or the available hypothesis to have a clear picture of the known latest research. Since decades Cardiologists are putting their efforts in understanding what are the possible risks and how to overcome them it was not really easy for them to finalize various Hypothesis. Thus, this field still provides wide opportunity for the young scientists to lay their efforts on finding out the proper mechanism in this not much explored medical condition.

This review tries to understand the major advancements that have happened in the research concerned to the Diabetic Cardiomyopathy. We have tried to have an overview on the Biochemical and Molecular reasons that support DCM.

Keywords: Diabetic Cardiomyopathy; Obesity

Introduction

Diabetic Cardiomyopathy is the one of those diseases that occurs to the heart muscles in the diabetic patients. It causes several disorders to the heart and it might also lead to the heart failure [1]. Patients in this condition can be seen as with the fluid accumulation either in lungs or legs. It’s been more than four decades that studies over Congestive heart failure were existing independent of the main reasons like age, obesity [2], CAD hypertension and hyperlipedemia [3]. Where, many researches had a common factor that all such patients shared a common medical condition termed diabetes. Studies enormously increased in understanding this pathological situation termed Diabetic Cardiomyopathy [4]. Some of the studies reported that diabetic patients have a lifetime increased risk of Heart failure when compared to other non diabetic Cardiac patients. 15-25% of the Heart failure patients in major clinical trials are been diagnosed to be diabetic. Framingham study [5] was the first known direct association that linked Diabetic Mellitus to Heart failure and also to put forward opportunity in exploring the increased risk of CM in Diabetic Cardiomyopathy (Figure 1).

Complexions seen in DCM Patients

One of the common symptoms noticed is Systolic dysfunction and its role in symptomatic heart failure, left ventricular dilation and atherosclerosis or hypertension [6].

Patients who are under type 2 diabetic [7] conditions have the more possibilities to get the cardiovascular mortalities. Diabetic Cardiomyopathy mainly affects to the Right ventricle, where one could notice the impaired systolic and diastolic functions in the type 2 diabetic conditions [8].

Figure 1: Pictorial representation of Normal and Cardiomyopathic Heart.

Diabetic Cardiomyopathy is known to have multi factorial pathogenesis, based on the following characteristics, i.e. Atherosclerosis, subclinical micro infarctions, mitochondrial dysfunction [9] and lipotoxicity [10]. Even hyperglycemic conditions in the Diabetic Cardiomyopathy could be seen in DCM patients [11]. Thus, DCM could also be termed as multifactorial pathological disorder. If the disease is in severe condition, there are fair chances of deposition of glucose in ventricles which ultimately leads to the hyperglycemia, which might also cause ventricular stiffness [12]. The glycation’s end product may yield fibrosis by cross-linking collagen; this would also increase the myocardial stiffness [13]. This also
Molecular Reasons: Genes involved in the DMC

The hyperglycemic conditions may change/induce the oxidative stress and it makes a number of secondary messenger pathways, finally causing cardiac hypertrophy, fibrosis and cell death.

Changes in the proteins and intracellular ions will harm the excitation-contraction coupling. Based on these conditions there are fair chances of acquiring some abnormalities, which leads to the autonomic responsiveness and autonomic neuropathy.

H-FABP Fatty acid-binding protein, heart and its related isoform (#40,42) could be up-regulated by 64% to 90% [17], tryptophan being oxidized at two regions of this protein. The masses of these modified peptides were depended on mono- and di-oxidation of tryptophan and kynurenine 3-Hydroxykynurenine (3-HK).

α-Myosin Heavy Chain (MHC) and its proteolytic forms maybe down regulated by 55-81% , where as the expression levels of β-MHC and its proteolytic forms were found to be increased by 61-75%, this is because of the presence of the ATPase than β-myosin, which are present in the cardiac MHC isoforms. Creatine kinase was also found to be reduced by 58-60% in the diabetic cardiomyopathy condition.

Biochemical Reasons concerned to DCM

The recognition of the disease was first noted by many aspects out of which one possible reason was alteration difference in diabetic hearts were metabolic disarrangements. Energy-efficient metabolic function in cardiac myocyte was observed in early 1950’s in diabetic patient with least or almost no carbohydrate oxidation. Though the symptoms are very close to ischemia [18], DCM patients were more prone to increased ischemic damages when compared to the non diabetic ischemic patients. The studies later suggested that the reason was diabetes lead to persistent hyperglycemia [19] and hyperlipidemia which alters heart metabolism by limiting the substrate availability. On the other side fatty acids, the substrate provide 70% of total ATP under normal conditions by oxidation in mitochondrial matrix i.e beta oxidation of fatty acid [20]. The heart chooses substrate based on the availability of substrate, energy demand and oxygen supplied which is major hindrance or the difference between normal and diabetic patients [21]. Cardiomyocytes also regulate their glucose uptake unlike other cells and are spared from the complications associated with hyperglycemia. They are good escapers unlike endothelial cells as they can internalize their insulin dependent Glucose Transporter GLUT4 which is strongly inhibited in type II Diabetes. The circulating lipids are indirectly known to increase citrate concentration which is strong inhibitor of phosphofructokinase in glycolysis [29]. And as we know when the rate of uptake take crosses the rate of oxidation immediately the fatty acids get shuttled to triglycerides synthesis pathway which although prevents lipotoxicity but reduces heart function. All the efforts of scientists who have provided immense evidences in concern to metabolism alterations add the reason for cardiac contractile dysfunction. In animal models experiments and study have provided clear picture that contractile dysfunction initially leads to diastolic dysfunction progressing towards systolic dysfunction ultimately leading to heart failure [30-35].

During diabetes these changes and alterations are progressed at much faster rate in cardiomyocytes leading to contractile dysfunction. The proper usages of metabolic modulators and preventive measures in early age have shown improved heart function. Thus it clearly visualizes that the diabetic Cardiomyopathy is not just a disease rather it is the encouraging medium for a faster disaster [36-38].

Challenging DCM: Treatment Advancements

The impaired myocardial blood flow resulted by endothelial dysfunction could be very well evidenced with the help of echocardiography [39]. However the major concerns to treat this condition would be to improve the blood flow, control diabetes, and reduce the symptoms and to protect the heart. The possible type of drugs any one could think of would be Angiotensins [40] converting enzyme inhibitors like Vasotec, Prinivil, etc., to dilate blood vessels for smooth flow of blood; Beta Blockers like Coreg, Zebeta, etc., to slow down the heart rate and have reduced Blood pressure; Diuretics like Lasis or as such to urinate more and also decrease fluid from lungs which help the individual to breathe more comfortably; Aldosterone antagonists like Aldactone to help heart work better [41]. Few drugs like Lanoxin are known to strengthen the heart muscle contractions, thus also reduces the heart failure risks.

Other advancements in the Treatment as per the recent studies reported are diverse. Trientine, a copper chelator treatment has shown to improve the cardiac function in diabetic animal models. Even Curcumin has shown high therapeutic effect against the DCM patients by attenuating oxidative stress [42]. It has also effectively worked by reducing cell death, inflammation [43,44]. Certain studies has evidenced that Glucagon-like Peptide-1 (Glp1) Receptor (Glp1r) agonists showed improved heart function and also developed potential to fight Myocardial infarction and ischemic hearts [45]. Echocardiography showed short term insulin therapy helped DCM patients to improve the cardiac function [46,47]. Few researchers also suggest that Diallylthrisulphide (DATS) have anti apoptotic effect which suppresses high glucose induced cardiomyocyte apoptosis by the inhibition of downstream JNK/NF-kB signaling and NADPH oxidase-related ROS [48,49]. Thus this might be a promising therapy for DCM patients [50-53].

Conclusion

Since Diabetic Cardiomyopathy has now become high prevalent, screening for its presence to the earliest would show much better opportunities to fight the condition and also might provide a better improvement at early diagnostics with the advancements we are able to avail today. Though there is enough research evidences available the demand for much advanced and curable therapeutics study is always unexplored. Thus as we understand with the above mentioned review
that Diabetic Cardiomyopathy patients have increased risk for the Heart Failure. The importance of regulating their diabetic control is very important for those patients to have a better cardiac function and reduced risks.

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References


