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A Short Literature Review on Diabetic Cardiomyopathy in Obese Conditions

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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).

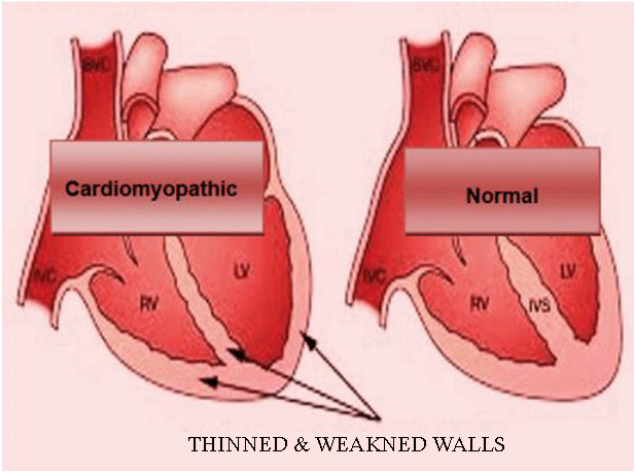

Figure 1: Pictorial representation of Normal and Cardiomyopathic Heart.

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].

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

decreases the LV end diastolic volume and results in the impairment of LV function. [14-16].

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-inefficient 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 escapists unlike endothelial cells as they can internalize their insulin dependent Glucose Transporter GLUT4 [22] and thus easily protect themselves from extracellular hyperglycemia [23-25]. The normal cardiomyocytes in diabetic heart not only showed decreased glucose uptake but also showed decreased lactate uptake, in short decreased carbohydrate uptake of which the mechanisms are still unclear, and due to this decreased glycogenolysis, the diabetic myocytes showed increased intracellular glycogen pool [26-28].

To the contrast due to reduced glucose uptake and thus reduced glucose oxidation rate, the beta oxidation shot up leading to cent percent ATP production. This can be easily judged by shot up in fatty transporter CD36 which could be used as biomarker in etiology of cardiac disease. A study also suggests that increase in fatty acids oxidation could also be related to alter signaling in insulin and hyperlipidemia, thus relating the cause to 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 Angiotensin [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 Lasix 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 have 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 Diallyltrisulphide (DATS) have anti apoptotic effect which suppresses high glucose induced cardiomyocyte apoptosis by the inhibition of downstream JNK/NF-κB 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

1. Elboudwarej O, Hojjat H, Safarpoor S, Vazirian S, Ahmadi S (2011) Dysfunctional HDL and Cardiovascular Disease Risk in Individuals with Diabetic Dyslipidemia. J Diabetes Metab S4: 001.
2. Yadav H, Jain S, Marotta F (2011) Probiotics Mediated Modulation of Gut-Flora Might Be a Biotherapeutical Approach for Obesity and Type 2 Diabetes. Metabolomics 1: 107e.
3. Figueroa A, Agil A (2011) Changes in Plasma's Oxidative Stress and Antioxidant Activity, Measured with Melatonin Levels, and its Relationship to Newborns from Obese and Diabetic Pregnancies. J Diabetes Metab S4: 002.
4. Fei J, Chen SY (2013) Splice Site Mutation-Induced Alteration of Selective Regional Activity Correlates with the Role of a Gene in Cardiomyopathy. J Clin Exp Cardiolog S12: 004.
5. Kengne AP, Turnbull F, MacMahon S (2010) The Framingham Study, diabetes mellitus and cardiovascular disease: turning back the clock. Prog Cardiovasc Dis 53: 45-51.
6. Marques JS, Almeida AG, David C, Luz-Rodrigues H, Diogo AN (2012) Copeptin for Discriminating Two-Year Mortality in Heart Failure Patients with Moderate to Severe Systolic Dysfunction. J Clin Exp Cardiolog S2: 006.
7. Niafar M, Nakhjavani M, Esteghamati A, Ziaie A, Jahed SA, et al. (2012) Efficacy and Safety of Insulin Glargine in Type 2 Diabetic Patients with Renal Failure. J Diabetes Metab 3: 189.
8. Francis GS (2001) Diabetic cardiomyopathy: fact or fiction? Heart 85: 247-248.
9. de O' Leary JC, Obregon D, Fernandez F, Tan J, Giunta B (2012) The Impact of HAART on Advanced Brain Aging: Implications for Mitochondrial Dysfunction and APP Processing. J Antivir Antiretrovir S10- 002.
10. Li R, Chao H, Ko KW, Cormier S, Dieker C, et al. (2011) Gene Therapy Targeting LDL Cholesterol but not HDL Cholesterol Induces Regression of Advanced Atherosclerosis in a Mouse Model of Familial Hypercholesterolemia. J Genet Syndr Gene Ther 2: 106.
11. Boudina S, Abel ED (2007) Diabetic cardiomyopathy revisited. Circulation 115: 3213-3223.
12. Kass DA, Bronzwaer JG, Paulus WJ (2004) What mechanisms underlie diastolic dysfunction in heart failure? Circ Res 94: 1533-1542.
13. Aronson D (2003) Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. J Hypertens 21: 3-12.
14. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, et al. (2000) Impact of diabetes on cardiac structure and function: the strong heart study. Circulation 101: 2271-2276.
15. Rijzewijk LJ, van der Meer RW, Smit JW, Diamant M, Bax JJ, et al. (2008) Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. J Am Coll Cardiol 52: 1793-1799.
16. Rijzewijk LJ, van der Meer RW, Lamb HJ, de Jong HW, Lubberink M, et al. (2009) Altered myocardial substrate metabolism and decreased diastolic function in nonischemic human diabetic cardiomyopathy: studies with cardiac positron emission tomography and magnetic resonance imaging. J Am Coll Cardiol 54: 1524-1532.
17. Milton Hamblin, David B. Friedman, Salisha Hill, Richard M. Caprioli, Holly M. Smith, et al. (2007) Alterations in the Diabetic Myocardial Proteome Coupled With Increased Myocardial Oxidative Stress Underlies Diabetic Cardiomyopathy. J Mol Cell Cardiol 42: 884–895.
18. Takeuchi N, Semba S, Naba K, Maeda T, Takada M (2012) Non-Occlusive Mesenteric Ischemia During the Course of Heart Failure. J Clin Case Rep 2: 220.
19. D'Ascenzo F, Moretti C, Longo G, Quadri G, Anselmino M, et al. (2011) Interactions between Hyperglycemia and Prior Ischemic Events in Patients Undergoing Percutaneous Coronary Revascularization: Contrasting Evidence from Bench and Bedside? Translational Medic 1: 102.
20. Shafiee-Kermani F, Grusak MA, Gustafson SJ, Lila MA, Niculescu MD (2013) Lower Concentrations of Blueberry Polyphenolic-Rich Extract Differentially Alter HepG2 Cell Proliferation and Expression of Genes Related to Cell-Cycle, Oxidation and Epigenetic Machinery. J Nutr Disorders Ther 3: 120.
21. Anwar AM, Mostafa MM, Nosir YFM (2010) Left Ventricular Remodeling in Diabetic Patients with and without Hypertension. J Diabetes Metab 1: 108.
22. Lehnen AM, Angelis KD, Markoski MM, Schaan BDA (2012) Changes in the GLUT4 Expression by Acute Exercise, Exercise Training and Detraining in Experimental Models. J Diabetes Metab S10: 002.
23. UNGAR I, GILBERT M, SIEGEL A, BLAIN JM, BING RJ (1955) Studies on myocardial metabolism. IV. Myocardial metabolism in diabetes. Am J Med 18: 385-396.
24. BING RJ, SIEGEL A, UNGAR I, GILBERT M (1954) Metabolism of the human heart. II. Studies on fat, ketone and amino acid metabolism. Am J Med 16: 504-515.
25. Li SH, McNeill JH (2001) In vivo effects of vanadium on GLUT4 translocation in cardiac tissue of STZ-diabetic rats. Mol Cell Biochem 217: 121-129.
26. Chatham JC, Gao ZP, Bonen A, Forder JR (1999) Preferential inhibition of lactate oxidation relative to glucose oxidation in the rat heart following diabetes. Cardiovasc Res 43: 96-106.
27. Higuchi M, Miyagi K, Nakasone J, Sakanashi M (1995) Role of high glycogen in underperfused diabetic rat hearts with added norepinephrine. J Cardiovasc Pharmacol 26: 899-907.
28. Oliver MF, Opie LH (1994) Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias. Lancet 343: 155-158.
29. Serfin J, Carragher J, Groman A, Dexter EU, Yendamuri S (2011) Outcome Prediction Using Markers of Aerobic Glycolysis (the Warburg effect) Varies Between Tumor Regions in Stage I Non-Small Cell Lung Cancer. J Mol Biomark Diagn 2: 116.
30. Finck BN, Han X, Courtois M, Aimond F, Nerbonne JM, et al. (2003) A critical role for PPARalpha-mediated lipotoxicity in the pathogenesis of diabetic cardiomyopathy: modulation by dietary fat content. Proc Natl Acad Sci U S A 100: 1226-1231.
31. Aasum E, Hafstad AD, Severson DL, Larsen TS (2003) Age-dependent changes in metabolism, contractile function, and ischemic sensitivity in hearts from db/db mice. Diabetes 52: 434-441.
32. Clerk LH, Rattigan S, Clark MG (2002) Lipid infusion impairs physiologic insulin-mediated capillary recruitment and muscle glucose uptake in vivo. Diabetes 51: 1138-1145.
33. Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, et al. (2000) Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci U S A 97: 1784-1789.
34. Stanley WC, Recchia FA, Lopaschuk GD (2005) Myocardial substrate metabolism in the normal and failing heart. Physiol Rev 85: 1093-1129.
35. Chatham JC, Forder JR (1997) Relationship between cardiac function and substrate oxidation in hearts of diabetic rats. Am J Physiol 273: H52-58.
36. Buchanan J, Mazumder PK, Hu P, Chakrabarti G, Roberts MW, et al. (2005) Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. Endocrinology 146: 5341-5349.

37. Golfman LS, Wilson CR, Sharma S, Burgmaier M, Young ME, et al. (2005) Activation of PPARgamma enhances myocardial glucose oxidation and improves contractile function in isolated working hearts of ZDF rats. Am J Physiol Endocrinol Metab 289: E328-336.
38. Shehata MF, Pater A (2011) Angiotensin-Converting Enzyme Inhibitors (ACE-Is) versus Angiotensin-Receptor Blockers (ARBs): Any superiority? J Hypertens Open Access 1: e101.
39. Moir S, Hanekom L, Fang ZY, Haluska B, Wong C, et al. (2006) Relationship between myocardial perfusion and dysfunction in diabetic cardiomyopathy: a study of quantitative contrast echocardiography and strain rate imaging. Heart 92: 1414-1419.
40. Macia-Heras M, Del Castillo-Rodriguez N, Navarro González JF (2012) The Renin-Angiotensin-Aldosterone System in Renal and Cardiovascular Disease and the Effects of its Pharmacological Blockade. J Diabetes Metab 3: 171.
41. Neerati P, Ravi Karan M, Kanwar JR (2012) Influence of Curcumin on Pioglitazone Metabolism and Pk/Pd: Diabetes Mellitus. J Diabetes Metab S6: 003.
42. Lukiw WJ, Bjattacharjee S, Zhao Y, Pogue AI, Percy ME (2012) Generation of Reactive Oxygen Species (ROS) and Pro-Inflammatory Signaling in Human Brain Cells in Primary Culture. J Alzheimers Dis Parkinsonism Suppl 2: 001.
43. Lu J, Pontré B, Pickup S, Choong SY, Li M, et al. (2013) Treatment with a copper-selective chelator causes substantive improvement in cardiac function of diabetic rats with left-ventricular impairment. Cardiovasc Diabetol 12: 28.
44. Yu W, Wu J, Cai F, Xiang J, Zha W, et al. (2012) Curcumin alleviates diabetic cardiomyopathy in experimental diabetic rats. PLoS One 7: e52013.
45. Younce C, Burmeister MA, Ayala JE (2013) Exendin-4 attenuates high glucose-induced cardiomyocyte apoptosis via inhibition of endoplasmic reticulum stress and activation of SERCA2a. Am J Physiol Cell Physiol.
46. Al Kadi HA, Alissa EM (2011) Prevalence of hyperlipidemia and associated risk factors among healthy young Saudi females: relationship with waist Circumference and body Mass Index. Endocrinol Metabol Syndrome S2: 001.
47. Faruk Akturk (2013) Valvular and Supravalvular Aortic Stenosis Secondary to Familial Hyperlipidemia. J Cardiovasc Dis Diagn 1: 102.
48. Carvalho AS, Guimaraes DD, Dantas BPV, Carreiro JN, Mendes- Junior LG, et al. (2012) Brain Angiotensin-II-derived Reactive Oxygen Species: Implications for High Blood Pressure. J Hypertens 1: 107.
49. Li Y (2011) Elevated Angiotensin II in Rat Nodose Ganglia Primes Diabetes-Blunted Arterial Baroreflex Sensitivity: Involvement of NADPH Oxidase- Derived Superoxide. J Diabetes Metab 2: 135.
50. Jankovic D, Winhofer Y, Promintzer-Schifferl M, Wohlschläger-Krenn E, Anderwald CH, et al. (2012) Effects of insulin therapy on myocardial lipid content and cardiac geometry in patients with type-2 diabetes mellitus. PLoS One 7: e50077.
51. Wang Y, Sun W, Du B, Miao X, Bai Y, et al. (2013) Therapeutic effect of MG-132 on diabetic cardiomyopathy is associated with its suppression of proteasomal activities: roles of Nrf2 and NF-Î°B. Am J Physiol Heart Circ Physiol 304: H567-578.
52. Chen W, Chen W, Xia Y, Zhao X, Wang H, et al. (2013) Therapy with Astragalus polysaccharides rescues lipotoxic cardiomyopathy in MHC-PPARÎ± mice. Mol Biol Rep 40: 2449-2459.
53. Kuo WW, Wang WJ, Tsai CY, Way CL, Hsu HH, et al. (2013) Diallyl trisufide (DATS) suppresses high glucose-induced cardiomyocyte apoptosis by inhibiting JNK/NFÎ°B signaling via attenuating ROS generation. Int J Cardiol 168: 270-280.