A Detailed Review on Diabetic Cardiomyopathy

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Abstract

Diabetic Cardiomyopathy is a clinical condition of ventricular dysfunction that occurs in the absence of coronary atherosclerosis and hypertension in patients with diabetes mellitus. It is characterized by diastolic dysfunction, which is defined as a defect in left ventricular relaxation leading to increased pressures and subsequent impaired filling during diastole. And present to the pathogenesis of diabetic cardiomyopathy. Diabetic cardiomyopathy is accelerated by the variation in the adaptive and innate immune systems. Diabetic cardiomyopathy is characterized by interstitial fibrosis, mainly composed of collagen, and perivascular fibrosis. In the review, we will discuss various aspects, aetiology, pathophysiology, and clinical manifestations of Diabetic Cardiomyopathy.

Keywords: Diabetic Cardiomyopathy, Diabetes Mellitus, Heart, Insulin, Clinical Condition

Introduction

Millions of people around the world live with diabetes mellitus. DM is recognized as the world's fastest-growing condition [1]. It is a metabolic disorder characterized by hyperglycaemia due to the impairment of insulin secretion and insulin action. It eventuates, when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces.

Classification of Diabetes [2]

As per the American Diabetes Association (ADA) in 1997, as T1DM, T2DM, GDM, and other types.

Type 1 diabetes (T1DM): In T1DM, the body produces either a very small amount of insulin or no insulin. T1DM is insulin dependent. It is due to the destruction of the pancreatic beta-cell. The hallmark of T1DM is the presence of autoantibodies against pancreatic islet beta cells. 80-90% of diabetes occurs in children and the number of youths diagnosed with T1DM according to the IDF in 2013. In the United States, 3 million people were diagnosed with T1DM in 2010. T1DM also produce some symptoms like polydipsia, polyphagia,

polyuria, extreme tiredness, sudden weight loss, enuresis, recurrent infections, wounds with slow healing, blurred vision, also the severe dehydration and diabetic ketoacidosis occurs in children and adolescents. Compared to adults these types of symptoms are more severe in children.

Type 2 diabetes (T2DM): It is the most common and most prevalent form of diabetes in the world. T2DM is a major risk for the development of cardiovascular disorders. The progression of T2DM changes occurs in the heart and blood vessels and it causes several different cardiovascular complications like coronary artery disease, stroke, peripheral arterial disease, and diabetic cardiomyopathy.

Gestational diabetes mellitus: It occurs during pregnancy. Each degree of glucose intolerance with onset or first recognition during pregnancy. As per the International Association of Diabetes with pregnancy study group (IADPSG) and American Diabetes Association (ADA), the high-risk women were found to have diabetes during their initial prenatal visit. Approximately 7% of all pregnancies are complicated by gestational diabetes and more than 200,000 cases are reported yearly. Diabetes is correlated with long-term damage, dysfunction, and failure of different organs, mainly the eyes, kidney, nerves, heart, and blood vessels. According to, the American heart association, diabetes is one of the crucial controllable risk factors for cardiovascular disease. People with diabetes increase a risk of many complications. Complications of diabetes included retinopathy, nephropathy, neuropathy, cardiomyopathy, etc.

Diabetic Retinopathy: It is the most common microvascular complication of diabetes mellitus. It depends on both the duration and severity of hyperglycaemia. It causes blindness and visual disability, caused by small blood vessel damage to the back layer of the eye and leading to the loss of vision. Comparatively 10,000 new cases of blindness to diabetic retinopathy in the "US". The histopathological sign of retinopathy with diabetes is a loss of pericyte. It also includes small haemorrhages in the middle layer of the retina. In India, the Chennai Urban Rural Epidemiology Study (CURES) reported an overall DR. Prevalence of 17.6% in patients with diabetic conditions. In South India, the Sankara Nethralaya DR Epidemiology and Molecular Genetic Study has estimated an urban prevalence of 18.0% and a rural prevalence of 10.3% of DR. In North Indian patients 21.0% prevalence of DR has been reported. According to National Health and Survey, the prevalence of diabetic retinopathy was 28.5% and 4.4% of loss of vision. Retinopathy was related to the incidence of MI and death from cardiovascular disease as per the world health organization's multinational study of vascular disease in diabetes.

Diabetic Nephropathy: It is also a microvascular complication of diabetes. It refers to the damage to the blood vessels of the kidney that occurs in people with diabetes. The pathophysiology includes increased glomerular basement membrane thickness and formation of micron aneurysm and includes other damage. In DN there are links between glucose control and the risk of developing this disease. It is treated by angiotensin-converting enzyme (ACE) and additional treatment of elevated blood glucose and the benefits of antihypertensive drugs. According to the study in 10 Asian nations or regions, 5549 patients with T2DM and 40% had microalbuminuria and 19% had macroalbuminuria. 12% of type 1 and 7% of type 2 diabetic patients found to be suffering from diabetic nephropathy. In the US 50,000 patients suffering from this disease in 2011.

Diabetic neuropathy: According to the ADA, diabetic neuropathy is a dysfunction of the nerve in people suffering from diabetes and is also associated with vascular and nonvascular abnormalities. It directly damages by hyperglycaemia. It also decreases the blood flow to the nerve which causes damage to the blood vessels. This mechanism can affect sensory loss and limb damage. DN is also affected on feet which leads to a decrease in the sensation in the feet. It is a very common complication of diabetes.

Diabetic Cardiomyopathy (4,5)

Diabetic cardiomyopathy is defined as the existence of abnormal myocardial structure and performance in the absence of other risk factors like coronary artery disease, hypertension, and significant valvular disease in individuals with diabetes mellitus. It is a typical and most prevalent complication of diabetes mellitus. The American Heart Association and European Society of Cardiology in collaboration with the European Association for the study of diabetes defined diabetic cardiomyopathy as a clinical condition of ventricular dysfunction that occurs in the absence of coronary atherosclerosis and hypertension in patients with diabetes mellitus in the year 2013. It is characterized by diastolic dysfunction, which is defined as a defect in left ventricular relaxation leading to increased pressures and subsequent impaired filling during diastole. Also characterized by lipid accumulation in cardiomyocytes, fetal gene reactivation, and left ventricular hypertrophy, leads to contractile dysfunction.

History of Diabetic Cardiomyopathy (6)

Despite decades of basic and clinical investigations, diabetic cardiomyopathy as a clinical entity remains elusive and ambiguous. It was first reported by Rubler in the year 1972. At that time some patients were diagnosed with diabetes and heart failure without arterial hypertension or coronary artery disease. By dissection of their heart, they found the heart revealed LV hypertrophy and fibrosis without confirmation of coronary artery atheroma. This clinical disease was examined as a "Diabetic Cardiomyopathy," this term was proposed by Danish Internist Lundback. In the year 1881, Leyden illustrated that heart failure was a "Frequent" and "Noteworthy" complication of diabetes, and Mayer concluded that heart disease in diabetes can be traced to an abnormality in metabolism. Diabetic cardiomyopathy was examined in White, Black, and Hispanic. According to the American Heart Association Statistics Committee and Stroke, the Statistics subcommittee declared that the prevention of heart failure was lowest in the Mexican- American subgroup followed by non-Hispanic whites and African Americans. As compared to non-Hispanics, Hispanics have more frequent heart failure with diabetes.

Epidemiology

1. Prevalence of diabetes (7)

According to WHO prevalence of diabetes increased over the few past decades in different countries or a part of the world. The prevalence of diabetes is different in a different country such as 3.8% in Africa, 7.3% in Europe, 10.7% in the Middle East and North Africa, 11.5% in North America and Caribbean, 9.6% in South and Central America, 9.1% in Southeast Asia, and 8.8% in western pacific.

Also, according to International Diabetes Federation (IDF), an estimated number of 425 million adults between the age group of 20 to 79 years were living with diabetes in 2017 and is estimated to increase to 629 million by 2045. The major contributor globally in 2017 for an increase in incidence and prevalence of diabetes is South East Asia which is estimated to increase by 84% by the year 2045 and is the highest among other countries globally.

India, China, and the USA are the top countries with the largest number of people living with diabetes. According to the Juvenile Diabetes Research Formulation, 40000 people with type 1 diabetes are diagnosed every year in the USA. Women who are diagnosed with gestational diabetes have a major risk of developing type 2 diabetes in the future with a 7.4-fold increased risk. About 90-95% of people are diagnosed with type 2 diabetes, and the largest number of people with type 2 diabetes is growing rapidly worldwide. So many people are still undiagnosed because there are few symptoms during the early year of type 2 diabetes.

2. Prevalence of cardiovascular disease (8)

Since 1975, in the United States, cardiovascular diseases are still the leading cause of death, it is about 633,842 deaths. Cardiovascular disease is also the cause of death globally with 17.7 million deaths in 2015. Calculated the indirect costs of $237 billion per year and a projected increase to $ 368 billion by 2035 so cardiovascular disease is considered as costly even ahead of Alzheimer's disease and diabetes as per the World Health Organization. Still, the risk of cardiovascular disease is high with a calculated 50% risk by the general population generally at the age of 45.

3. Prevalence of diabetes and cardiovascular disease (9)

Prevalence of diabetes and cardiovascular disease at a different age: At younger age and middle age in high and middle-income countries: People who are suffering from diabetes living in high- middle-income countries. The prevalence of cardiovascular diabetes ranged from 2.6% to 16.2 % in high-income countries. The people with type 2 diabetes along with cardiovascular disease, the mean age of the population was between 56 and 66 years with prevalence ranging from 14.8% to 40.5%. Furthermore, for people with diabetes along with stroke, the mean age of the population was between 53 and 57 years with prevalence ranges from 3.5 to 10.4 % in high and middle-income countries.

Mortality of cardiovascular disease along with diabetes in middle-aged people: Out of 1000 people, 2 to 27 people died from cardiovascular disease along with type 2 diabetes and unsatisfied diabetes and the mean age of study population was between 49 to 69 years.2 to 7 people died from coronary artery disease and 1 to 9 people died from a stroke in middle-aged people. With age, the mortality rate increased.

4. Prevalence of diabetic cardiomyopathy (DCM) (10)

With the increase in the prevalence of diabetes, there is also an increase in the risk of most of the population suffering from diabetic cardiomyopathy. Patients suffering from type 2 diabetes are at two to two and a half fold greater risk of developing cardiovascular complications. The Framingham Study was the first epidemiologic landmark stating the link between diabetes and heart failure (HF).

According to the study patients having diabetes have a 2.4-fold increased risk of HF in men and 5-fold in women irrespective of advancing age and predisposing disease. On the contradictory, only a few statistics are available on the association of the development of DCM due to fewer patients suffering from type 1 diabetes compared to type 2 diabetes. According to a study performed based on data from the Swedish national diabetes registry incidence of HF per 1000 patients was found to increase uniformly. Also, in a registry-based study performed by Rosengren et. al. incidence rate for diagnosis of HF was 4 per 1000 diabetic patients.

Etiology (11)

There are some abnormalities of diabetes along with the development of heart failure.
Some risk factors for diabetic cardiomyopathy are as follows

1. Obesity (12)

Obesity affects type 2 diabetes, hypertension, dyslipidaemia, and atheroma, which leads to premature death in obese people. It is one of the most known cardiovascular risk factors. It occurs by excess fat deposited subcutaneously around the abdomen and within the visceral cavity, which is commonly found in type 2 diabetic patients. It associates with insulin resistance and a highly atherogenic risk profile. Adipose tissue produces non-esterified fatty acids and TNF-α (cytokines) which is contributed to insulin resistance and atherogenesis. Reduced levels of adiponectin, an insulin-sensitizing protein whose secretion by adipose tissue is paradoxically decreased in obesity may also contribute to insulin resistance and DCM.

2. Hyperglycaemia

Hyperglycaemia plays a crucial role in the initiation of diabetic vascular complications by several mechanisms. The levels of upstream glycolytic metabolite glyceraldehyde 3- phosphate are increased; activate the AGEs pathway through forming the major intracellular AGE precursor methylglyoxal from glyceraldehyde 3-phosphate. Another one, the classic PKC pathways are activated whereas the activator of PKC, diacylglycerol is formed from glyceraldehyde 3- phosphate. Furthermore, it increased the levels of glycolytic metabolite fructose -6- phosphate and increased glycolysis which leading to a pronounced flux through the hexosamine pathway and resulting in conversion by using the enzyme glutamine: fructose-6- phosphate amidotransferase. At last, the inhibition of glyceraldehyde-3-phosphate. As per this hypothesis, the above pathogenic mechanisms are linked by a single, unifying, hyperglycaemia-induced process which is observed as the path mechanism underlying insulin resistance, cardiovascular diseases, diabetes, and its complications. Hyperglycaemia causes significant functional alteration to the cellular $Na+ – Ca2+$ ionic channel and decreased extrapolation and an increased intracellular concentration of ionic calcium. Further, the dysfunction of cellular

Na+ - K+ channel, is increasing the intracellular sodium. It also increases intracellular calcium in cardiac myocytes. Formation of AGEs causing thickening and leakage of vasculature and forming irreversible and abnormal deposits of plasma-derived proteins in the myocardial subintimal arterial layers. AGEs generate toxic reactive oxygen species (ROSs) that impair cellular interaction and damage myocardial vascular function, causing endothelial vasomotor dysfunction AGEs effects intruded by specific receptors (RAGE) which is expressed by vascular endothelial, smooth muscle cells, and cardiac myocytes. AGE-RAGEE interaction which leads to the up-regulation of procoagulant and adhesive proteins with the inclusion of tissue factor, plasminogen activator inhibitor-1 (PAI-1), and vascular cell adhesion molecule- 1 (VCAM-1) in the cardiac endothelium. Due to the expression of VCAM-1, an increase in monocyte adhesion. Although the monocytes expressing RAGE are initiated by chemotaxis to sites AGE accumulation. Afterwards, they infiltrate the myocardial sub-endothelium to form foam cells, an early step in atherogenesis. Further, the extracellular RAGE ligands which are the RAGE-binding proteins that collaborate with RAGE on cardiac myocytes to produce the various expression like tumour necrosis factor-α (TNF-α), VCAM-1, nuclear factor kβ (NF-kβ) and interleukin 1. Therefore, modulating the inflammatory component of cardiovascular disease through the cytokine cascade. Furthermore, hyperglycaemia activates the reactive oxygen species (ROS) by inducing glucose oxidation and generating mitochondrial superoxide. Later ROS triggers matrix metalloproteinase 9 (MMP9) and degradation of the extracellular matrix which increases the matrix turnover, attenuates Sarco - endoplasmic reticulum- calcium ATPase-2 (SERCA-2) and alters the expression of different miRNAs which leads to contractile dysfunction and conclusively diabetic cardiomyopathy (DCM). Initiation MMP9 increases inflammation through inducing pro-inflammatory tumor necrosis factor α (TNF-α) and mitigating the anti-inflammatory interleukin-10 (IL-10) and cytokines in diabetes which aggravates diabetic cardiomyopathy (DCM). Another mechanism, the differential expression of some miRNAs which induces TNF-α inhibits the IL-10 and regulates the inflammation. Some miRNAs like miR-155 and miR-223 act as an inflammatory and cardioprotective. The generation of superoxide which also causes DNA damage that activates the reparative enzyme poly ADP ribose polymerase (PARP), PARP debilitates glyceraldehyde phosphate dehydrogenase and alters glucose from the glycolytic pathway into alternatives pathways like advanced glycation end product (AGEs) and protein kinase C (PKC) which decrease calcium regulating receptor, enzyme ryanodine receptor and also the SERCA-2. Reducing the contractility of cardiomyocytes and inducing the ventricular stiffness which leads to diabetic cardiomyopathy (DCM). (13) The metabolic and molecular changes in myocardial cells and increased glucose metabolism due to hyperglycaemia which leads to an increase in oxidative stress by the generation of reactive oxygen species (ROS) from mitochondria. Moderation of myocardial contractility and ultimately myocytes fibrosis due to the overproduction of superoxide by the mitochondrial respiratory chain and subsequent oxidative stress. Further, the DNA damage and acceleration of cardiomyocyte apoptosis due to the ROS and oxidative stress. Also, the activation of poly ADP ribose polymerase (PARP), a DNA reparative enzyme by the DNA damage which is induced by oxidative stress. After that PARP diverts glucose metabolism from its glycolytic pathway which is through inhibition of glyceraldehyde phosphate dehydrogenase into the alternative biochemical pathways which result in the generation of many mediators that leads to cellular injury which is induced by hyperglycaemia. Also include the AGEs, increased flux of hexosamine and polyol, and the activation of the enzyme protein kinase c (PKC). Increase the AGEs in diabetic subjects by the oxidative stress which has been induced by chronic hyperglycaemia and AGEs can covalently crosslink different intracellular and extracellular proteins which is act as a pivotal factor in diabetic complications and that crosslink in collagen and elastin which results in increased the myocardial stiffness and impaired cardiac relaxation. And AGEs are also found to be inducing the myocardial damage in animals and in humans. Through the interacting and up-regulating the receptors including receptors of AGEs and galectin-3, AGEs exert their detrimental effect on the myocardium and activation of transcription factors like nuclear factor –KB (NF-KB). And it triggers some pathways that induce the production of pro-inflammatory cytokines like TNF-α and cause myocardial damage. Due to chronic hyperglycaemia, increased flux of glucose into the alternate metabolic pathway that is a hexamine pathway that is implicated in some adverse consequences of diabetes. In this pathway, increased glucose metabolism which is associated with disruption of normal cardiomyocytes calcium flux linked to decrease the sequestration of calcium in the sarcoplasmic reticulum and it leads to a reduction in myocardial

performance and impaired the diastolic relaxation. This is a possible mechanism for diabetic cardiomyopathy. In the presence of nicotinic acid adenine dinucleotide phosphate (NADPH) that is oxidized to NADP+, glucose is converted into sorbitol by the action of enzyme aldose reductase. This NADPH act as a factor essential for the regeneration of reduced glutathione, also the scavenger of ROS in the body, and increased utilization of NADPH in the polyol pathway that disturbs the redox balance of cells and this polyol pathway also activated by chronic hyperglycaemia. DNA damage and cardiomyocyte apoptosis due to the increase in oxidative stress and sorbitol can glycate proteins that lead to the formation of AGEs, which are mediators of tissue injury in diabetes.

3. Insulin resistance (12)

Insulin resistance and hyperinsulinemia also play a major role as risk factors for diabetic cardiomyopathy. Due to insulin resistance and hyperinsulinemia, an imbalance in the direct effect of insulin action occurs. Insulin resistance and hyperinsulinemia are also associated with a bunch of thrombotic risk factors like elevated levels of PAI-1, factor VII, factor XII, and fibrinogen. Insulin resistance and hyperinsulinemia increase systemic metabolic disorders and activate the SNS, RAAS, prompt oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress and impair calcium homeostasis. Which results in cardiac fibrosis, hypertrophy, cardiomyocyte death, dysfunction of the coronary microcirculation, and eventually heart failure. Pathophysiological changes in cardiomyocytes underlie the risk factors for insulin resistance and hyperinsulinemia and result in a potentially vicious cycle. [Ca2+] i, Ca2+ influx; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system. Insulin resistance also associated with the combination of established and emerging risk factors, and including hypertension and C- reactive protein. Which is an acute phase inflammation marker that leads to an increased risk for diabetic cardiomyopathy Association between increased level of C- reactive protein and LV myocardial performance Also as a risk factor for atherosclerosis and cardiovascular disease with the metabolic syndrome. On the diabetic heart, the effect of insulin is related to both systemic metabolic abnormalities and the direct effect of insulin action on the vasculature. Furthermore, the elevation and imbalance of cardiovascular and atherothrombotic metabolites and cytokines which are related to insulin resistance and hyperinsulinemia play a major role in the pathogenesis of diabetic cardiomyopathy. The direct action of insulin on the vasculature, mediate a combination of proatherogenic and antiatherogenic effect with endothelial function and smooth muscle cell growth. Hyperinsulinemia leads to cardiomyocyte hypertrophy by various mechanisms. Brain natriuretic peptide (BNP), a biomolecule released from the ventricles in response to myocardial stretch, which has been increased in patients with heart failure. And also play an important molecular marker of cardiac hypertrophy and its gene expression significantly higher, with animal models of hyperinsulinemia and insulin resistance. Left ventricular hypertrophy and increased left ventricular weight was also found in these animal models. It also acts as a biomarker for screening subclinical ventricular diastolic dysfunction in patients suffering from uncontrolled diabetes. In diabetes hypertrophy of cardiac myocytes, regulated at the transcriptional level. Different genetic and epigenetic alterations resulting from hyperinsulinemia leads to activation of multiple transcription factors that modulate cellular and extracellular protein expression. And activation of such transcription factors which have been shown to result in cardiomyocyte hypertrophy and deposition of extracellular matrix proteins. Two insulin signaling pathways are involved. The first pathway involves insulin receptor substrate 1 (IRS1), and this is acts upstream of the phosphatidylinositol 3kinase (PI3K)–protein kinase B which is also called as AKT. Signal transduction pathway to elicit predominantly metabolic responses. Furthermore, the activation of AKT increases the glucose uptake in the heart along with the translocation of GLUT4 to the cell membrane of cardiac cells. Endothelial nitric oxide synthase activated by the PI3K–AKT which increases in bioavailable nitric oxide mediates coronary vasodilation, myocardial substrate flexibility, and energy homeostasis. The second pathway involves signal transduction through mitogen activated protein kinase (MAPK) which contributes to growth and remodelling responses and the resultant myocardial hypertrophy, cardiac fibrosis, impaired myocardial–endothelial signaling and death of myocardial and endothelial cells. Therefore, insulin signaling in the heart constitutes a highly complex network with multiple feedback loops and crosstalk. Due to the action of the

MAPK pathway, insulin-resistant states exhibit an imbalance in the metabolic and growth effect of insulin signaling. Further, increased phosphorylation of serine of the critical insulin signaling factor IRS-1 which leads to impaired PI3K engagement and the stimulation of AKT. Various activation by changes in oxidation-reduction state or nutrition-related factors, some serine kinases which can reduce compact of IRS and PI3K through phosphorylation of serine residues on IRS-1/ IRS-2 Overnutrition and renin-angiotensin-aldosterone system activation are increasingly appreciated as having an interactive activity on the stimulation of mechanistic target of rapamycin (mTOR)–S6 kinase 1 (S6K1) signaling, which, results in reduces insulin metabolic signaling such as IRS1 and IRS2 and PI3K–AKT in cardiovascular tissues. The cardiac insulin resistance is a metabolic and functional disorder that is often associated with obesity and the development of diabetic cardiomyopathy. Insulin resistance and hyperinsulinemia are related to the stiffness of both the large and small blood vessels. The increased plasma levels of insulin and that are features of hyperinsulinemia which increase the distinction of vascular smooth muscle cells to an osteoblast-like phenotype and contribute to the observed increase in vascular stiffness. Furthermore, raised insulin levels might also promote vascular stiffness by increasing alkaline phosphatase activity, osteocalcin expression, and the formation of mineralized nodules in vascular smooth muscle cells by increased levels of receptor activator of nuclear factor κB. Therefore, impaired endothelial cell and vascular smooth muscle cell function are related to an increased risk of developing coronary artery disease in association with diabetic cardiomyopathy.

4. Free fatty acid (13)

Due to the elevation in nonesterified fatty acids which is also called free fatty acid, a metabolic disturbance occurs. As a source of energy, the heart is capable to utilize FFA as well as carbohydrates. FFA is a superior source of energy, and this initiates carbohydrates with increased starvation, and this is occurring because of fetal gene reprogramming. In the diabetic heart, energy production through glucose utilization may be decreased and increased FFA utilization. It leads to the depletion of glucose transporter (GLUT)-1 and -4.34. In diabetic mice, restored cardiac metabolism and function due to the transgenic expression of GLUT-4. And it suggested that glucose metabolism stimulates fatty acid uptake in the mitochondria. It also promotes the mitochondrial uncoupling of oxidative phosphorylation with an increase in long-chain acylcarnitines and decreased myocardial high energy reserves and contractile dysfunction. The elevated level of FFA repeals pyruvate dehydrogenase which actuates the accumulation of glycolytic intermediates and ceramides and it promotes apoptosis. Due to the toxic metabolites from FFA open K-ATP channels which cause lipotoxicity and diminish the capability of cardiomyocytes to synchronize calcium use, which causes contractile dysfunction and initiation of apoptosis, hypertrophy, and contractile dysfunction which leads to diabetic cardiomyopathy. The contribution of glucose oxidation to cardiac energetics is less than normal among patients with obesity and Type 2 diabetes mellitus. The fatty acid metabolism is increased to join the myocardial energy needs. Further, the plasma FFA levels in patients having type 2 diabetes mellitus and obesity cause increased cardiac fatty acid uptake and triglyceride agglomeration. Due to the extravagant Fatty acid delivery and uptake by cardiomyocytes. It is likely to eclipse mitochondrial oxidative capacity and in consequence, lead to lipotoxic cardiac injury. The extravagant fatty acid enters non-oxidative pathways and produces fatty acid intermediates like ceramide. In mitochondria, increased Fatty acid oxidation is related to an accumulation in the generation of ROS that oxidizes cytoplasmic lipids into lipid peroxides. The ROS and lipid peroxides in turn cause cellular and mitochondrial damage and the uncoupling of mitochondrial oxidative metabolism. Therefore, reduced myocardial generation of energy and decreased cardiac contractility. Also decreased production of energy leads to reduced myocardial calcium handling which leads to cardiac dysfunction.

5. Hypertension

Hypertension is a major risk factor for the vascular system and coexists with types of diabetes such as type 1 and type 2 diabetes. Also increased risk of cardiovascular complications. It is higher in patients who are suffering from diabetes along with its complications such as diabetic cardiomyopathy. The fundamental cause of hypertension and diabetic cardiomyopathy is insulin resistance. Hypertensive also altered glucose metabolism. According to the study, Morales et al. concluded that the hypertensive had a significantly higher incidence of impaired glucose tolerance and type 2 diabetes as compared to normotensive subjects. Approximately 15% of hypertensive develop type 2 diabetes. Therefore, elevated blood pressure is recognized

as a risk factor for diabetes. Also, 35-75% of diabetes along with its complications can be imputed to hypertension. Blood pressure measurement is easy to measure in the clinical setting, mainly the blood pressure cut-off for treatment and diagnosing purposes; hypertension is generally accepted to be systolic blood pressure ($\geq$ 140 mm/Hg) and diastolic blood pressure ($\geq$ 90 mm/Hg). Also, some of these cut-offs are for those already at risk for cardiovascular disease. Further, hypertension and diabetic cardiomyopathy are collaborating and share the same pathogenetic pathways. The indicative of insulin resistance that contributes to diabetic cardiomyopathy. It may also impart to hypertension. Another study reported that the fibrates used to treat hypercholesterolemia and decrease the prevalence of hypertension (25-112%).

6. Cardiac autonomic neuropathy (14)

It is illustrated in both type 1 and 2 diabetes mellitus and it is a common complication of diabetes which cause abnormalities in heart rate and vascular hemodynamic. Also diagnosed with abnormal differentiation in diurnal and nonfactual blood pressure, resting heart rate disorder, exercise intolerance, and extended of QT interval in ECG. In the history of diabetes, the prevalence of cardiac autonomic neuropathy is 60%. Cardiac autonomic neuropathy influence blood flow in the coronary vasculature and changes the contractile function of the myocardium. The reduction of beta-1 and 2 adrenergic receptors is also related to diabetic cardiomyopathy. The changes in myocardial autonomic neurotransmitters cause toxic effects on catecholamine and apoptosis which is imparted to diabetic cardiomyopathy. Further, the microenvironment of the myocardium is changed in the heart of diabetes and it is involved in deformed cardiac progenitor cell growth and association which contributes to diabetic cardiomyopathy.

Pathophysiology (15)

The pathophysiological mechanism of diabetic cardiomyopathy has not been adequately interpreted. The phenomenon of diabetic cardiomyopathy is multifactorial. There are different suggested mechanisms including insulin resistance, microvascular impairment, subcellular component abnormalities, metabolic disturbances, cardiac autonomic dysfunction, alterations in the renin-angiotensin-aldosterone system (RAAS), and maladaptive immune responses. Also includes oxidative stress, myocardial dysfunction, inflammation, and other mechanisms.

1. Oxidative stress and myocardial dysfunction (16)

Oxidative stress is a major variation between the production of reactive free radicals and antioxidants and its damage caused by ROS and RNS which has been appeared to Mitochondrial dysfunction and oxidative stress are usually relevant to the cardiovascular diseases. Mitochondrial dysfunction is thoroughly related to ROS formation and has been evaluated to play a major role in the development of diabetic cardiomyopathy. In diabetic cardiomyopathy, the hyperglycaemia and FA oxidation in mitochondria, stimulate reactive oxygen species agglomeration in cardiomyocytes. And these are involved in all the stages of diabetic cardiomyopathy. Too much of ROS encourage the uncoupling of oxidative metabolism, influence DNA, protein and lipid oxidative damage, triggers NF-KB activation and activate to endoplasmic reticulum (ER) stress. As a conclusion, myocardial energy generation is impaired, disturbed the calcium handling, and decreased the cardiac contractility and efficiency. Oxidative stress directly induces insulin resistance through the up-regulation of extracellular signal-regulated protein kinase (ERK1/2) activity, which retards the NF-E2 related factor 2 (Nrf2) and a transcription factor that protects against sustained oxidative stress in the murine cardiomyocytes. The ROS accumulation also accelerates the cardiomyocyte apoptosis. This is frequently detected in the myocardium of animal models and the patients having diabetes. Apoptosis is caused by different mechanisms, which include the activation of DNA reparative enzymes like poly (ADP-ribose) polymerase (PARP) and by the inference with nitric oxide metabolism. The PARP also actuates the NF-KB and causes glucose metabolism from its pathway such as the glycolytic pathway. Therefore, the hyperglycaemia-induced cell injury. The ensuring assembling of glycolytic intermediates will, in turn, impair cardiac tissue beyond AGE formation and protein kinase C activation.

2. Role of inflammation (17)

The inflammation is frequently related to obesity and type 2 diabetes mellitus. And present to the pathogenesis of diabetic cardiomyopathy. The activation of different signalling pathways like, NF-kB, c-jun NH2-terminal kinase, p38- MAPK, which could moderate a state of inflammation and that is linked to insulin resistance, therefore, it played a crucial role in diabetic complications. The most significant mediators of the inflammatory process are NF-kB. The activation of NF-kB is related to the expanded release of cytokines like tumour necrosis factor-alpha (TNF-α), which is frequently elaborated in cardiac damage and causes to NF-kB activation, consequently contributing to the intensification of side effects in the heart with diabetes. Promoted the inflammatory mediators which lead to insulin resistance if they decreased the IRS-1 tyrosine phosphorylation, also the activation of PI3K and AKT, and reduced insulin signalling. Besides, elevated inflammatory markers may aggravate insulin insufficiency by impairing β-cell mass. Upgraded inflammatory cytokines, like TNF-α, interleukin (IL)-6, cell adhesion molecule, along with vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1(ICAM-1), acute phase reactants, like C-reactive protein (CRP), PAI-1 and other biological markers of inflammation which have been found in circulation and the diabetic hearts of patients with type 2 diabetes mellitus.

According to some data, the elevated levels of some inflammatory markers like IL1-β and TNF-α, are involved in diabetic cardiomyopathy and improve epicardial thickness and encourage myocyte contractile dysfunction, therefore depressing myocardial function and contributing to heart failure. Additionally, cardiac overexpression of TNF-α has been correlated with cardiac hypertrophy and fibrosis also with LV dysfunction. Moreover, the extreme production of IL-6 can stimulate LV dysfunction and cardiac hypertrophy under acute myocardial infarction. While the inflammatory response appears to relate to diabetic cardiomyopathy development, its existence and impact vary in the early and the long-standing stages of the disease. thus, as per Ares-Carrasco et al, using normotensive and spontaneously hypertensive rats with T1DM which is induced by streptozotocin, myocardial fibrosis and apoptosis are features of myocardial damage secondary to long-term experimental diabetes, even so, inflammation was regulated by the expression of anti-inflammatory molecules, in particular IL-10, and antioxidants. And found interesting effects when diabetes coexisted with hypertension. DCM and hypertensive cardiomyopathy share a few typical features which include functional and structural changes that provide to cardiac tissue impairment. According to the additional proteomics studies of AresCarrasco et al in SHR and SHR/DM1 rats, when diabetes and hypertension attend hearts present with impaired expression of metabolic, hypertrophic, and apoptotic proteins, in difference with the early stages of injury, and fibrotic and inflammatory rates are not accompaniment. A further factor that plays an important role in the modulation of inflammation in diabetic cardiomyopathy disturbs the RAAS activation. Ang II not only influences vasoconstriction, cell growth, and oxidative stress but also stimulates inflammation. And capable to actuate cytokine release, and stimulating the production of PAI-1 and pro-inflammatory transcription factors, like NF-κB. Which in turn modulates adhesion molecules (VCAM-1 and ICAM-1) and the expression of several cytokines, as earlier on mentioned.

3. RAAS: - Renin-angiotensin-aldosterone system (18)

The important role of RAAS in diabetes-induced cardiac dysfunction. It is a hormonal cascade that plays a critical role in the homeostatic control of arterial pressure by controlling blood vessel constriction. Also, the deregulation of RAAS plays a significant role in the pathological origin of renal disease, cardiovascular diseases, and arterial hypertension. Furthermore, the contributes to the development of cardiomyopathy. Additionally, the activation of the RAAS, locally as well as systemically, is strongly related to the development of insulin resistance and type 2 diabetes mellitus. Extravagant activation of RAAS also has been described in diabetes. And that it has appeared to be correlated with some of the hallmarks of diabetic cardiomyopathy, like increased fibrosis, angiogenesis, oxidative damage, and the cardiomyocyte, endothelial cell apoptosis, and necrosis and this over-activation has been admitted as a significant factor in the progression of the disease. The main physiological effector molecule of RAAS is angiotensin II (Ang II) and its release in the myocardium. Further, the diverse and widespread actions affect cardiac function because of the up-regulation of RAAS. The increase of Ang II in diabetic rats has been associated with cardiomyocyte hypertrophy and apoptosis and stimulates the proliferation of cardiac fibroblast and synthesis of collagen, which causes myocardium

interstitial and perivascular fibrosis, ventricular myocardium rigidity, and impaired diastolic function, which causing to the clinical symptoms of diabetic cardiomyopathy.

4. Maladaptive immune response

Diabetic cardiomyopathy is accelerated by the variation in the adaptive and innate immune systems. The stimulation of macrophage polarization to classic (M1) or alternative (M2) phenotypes and pro-inflammatory T helper cells repeatedly occurs in states of insulin resistance or obesity. However, the persistent overfeeding influence immune responses that provide to low-grade inflammation within white adipose tissue. The macrophage M2 polarization is an anti-inflammatory response while M1 polarization is a pro-inflammatory response in insulin-resistant and obesity states. M1 macrophages secrete inflammatory cytokines, which decrease cardiac and systemic insulin signaling and enable the development of diabetic cardiomyopathy. In contrast, M2 macrophages secrete macrophage mannose receptor 1 and interleukin 10 and decrease the development of myocardial fibrosis and cardiomyocyte hypertrophy. The further population of immune cells (T helper lymphocytes) was recognized in diabetic patients along with its complications such as diabetic cardiomyopathy. As compared to mice fed a high-fat diet and lean mice, a higher CD8+: CD4+ T-cell ratio is found in the visceral adipose tissue. Diet-induced insulin resistance also induces a dramatic increase in type 1 T helper-polarized cells, while the type 2 T helper-polarized fraction is reduced by ~50%. The elevated secretion of chemokines, growth factors and proinflammatory cytokines by T helper lymphocytes results in increased impaired diastolic relaxation and cardiac fibrosis. Thus, the regulatory T-cells usually reduce the proinflammatory effects of T helper cells in the heart.

Clinical Manifestations of Diabetic Cardiomyopathy (19)

1. Structural changes

a. Left ventricular hypertrophy

Diabetes is an unconventional contributor to left ventricular hypertrophy (LVH) and myocardial stiffness. This also suggests that structural alterations of the heart in patients with diabetics are not an early defect but, a sooner consequence of changes related to diabetes-like hyperglycaemia or obesity also retinopathy and nephropathy related to T1DM can affect myocardial remodelling. Additionally, in T2DM increased left ventricular mass is an independent marker of cardiovascular risk that frequently occurs independently of arterial blood pressure. According to Framingham's study, investigators reported that eventually an increase in left ventricular wall thickness in women with diabetes and confirmed that women with diabetes, had a steeper enhancement in left ventricular mass as compared to men and also without diabetes. Furthermore, another study, the Strong Heart study reported that the population of American Indians found that men, as well as women along with diabetes, had greater left ventricular mass and wall thickness. Furthermore, in a multi-ethnic population, the likelihood of having left ventricular mass above the 75th percentile of the distribution was 1.5-fold greater in patients with type 2 diabetes, independently of various covariates, including hypertension. In this same population, it was shown that increased left ventricular mass can be seen only in patients with diabetes, as compared with patients with impaired or normal fasting glucose concentrations. Suggesting that alterations in the geometry of the heart in diabetic individuals are not an early defect but, rather, a consequence of changes associated with diabetes such as hyperglycaemia or obesity.

b. Interstitial fibrosis

Diabetic cardiomyopathy is characterized by interstitial fibrosis, mainly composed of collagen, and perivascular fibrosis. Regan et al found a significant increase in the deposition of collagen around the vessel and between the myofibers in heart biopsies from diabetic patients. Besides, a significant increase in collagen type III, but not type I or VI, was found in endomyocardial biopsies obtained from patients with type 2 diabetes, free of CAD and hypertension. Furthermore, diastolic dysfunction detected in a population of patients with uncomplicated type 2 diabetes correlated with pro-collagen type I carboxy-terminal peptide, suggesting a mechanistic involvement of myocardial fibrosis in the myocardial dysfunction that occurs in diabetes. Also, perivascular fibrosis and collagen deposition are primary structural changes of diabetic cardiomyopathy.

c. Increased cell death and oxidative stress

Diabetic myocardium is susceptible to higher myocyte cell death by apoptosis and necrosis. Studies recommended that hyperglycaemia results in the production of reactive oxygen species, contributing to accelerated apoptosis. Apoptosis was maximally induced in the diabetic myocardium, whereas hypertension exaggerated the process of necrosis. Although most 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 hyperglycaemia.

d. Myocardial lipotoxicity

Diabetic cardiomyopathy is also characterized by increased deposition of lipids in the myocardium, which can contribute to cell death and cardiac dysfunction. There is a 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.

2. Functional changes

In DCM, some functional changes evolve and progress. It is therefore incumbent upon clinicians to identify these abnormalities because early detection and appropriate treatment can prevent the worsening of this condition to overt heart failure.

a. Diastolic dysfunction

Diabetic cardiomyopathy in humans is characterized by diastolic dysfunction, which may precede the development of systolic dysfunction. Indeed, echocardiography performed in 87 patients with type 1 diabetes mellitus without known CAD revealed diastolic dysfunction as indicated by reduced early diastolic filling, increased atrial filling, extended isovolumetric relaxation, and increased supraventricular premature beats. Similarly, in individuals with uncomplicated type 1 diabetes without clinically apparent macrovascular or microvascular complications, Carugo et al, reported an age-related increase in diastolic diameter. Similar approaches in patients with well-controlled type 2 diabetes revealed a prevalence of diastolic dysfunction in up to 30%. The use of flow and tissue Doppler techniques suggests an even greater prevalence of diastolic dysfunction (as much as 40–75%) in individuals with type 1 and type 2 diabetes without overt CAD. Indeed, indices for diastolic dysfunction such as E/E0 and E/A0 ratios were impaired in patients with type 2 diabetes.

b. Systolic dysfunction

Systolic dysfunction is an impairment in the ability of the heart to eject blood. 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 only 6% of those free from complications. Also, a subtle systolic dysfunction, which is usually characterized by a low left ventricular ejection fraction (LVEF), is seen.

c. Impaired contractile reserve

DCM involves some stages of the disease, which include a period in which symptoms are not present, and resting left ventricular dimension and function are still normal. In this early phase, left ventricular dysfunction can be characterized by exercise. Indeed, impaired augmentation of LVEF occurs in as many as 40% of patients with diabetes. Recent reports in both type 1 and type 2 diabetes showed that longitudinal functional reserve and left ventricular contractility were reduced after exercise. Whereas no change in these parameters was observed at rest. Thus, cardiac performance after exercise could be a tool with which to detect early contractile dysfunction in diabetes.

d. Metabolic changes

Several Studies of altered cardiac metabolism in animal models of diabetes have come out in recent years, becoming a desirable mechanism contributing to the development of DCM. In this section, we will discuss the recent findings supporting the existence of altered cardiac substrate metabolism and mitochondrial dysfunction in the heart of humans with diabetes.

Conclusion

In this review, we summarize Diabetic Cardiomyopathy. Diabetic cardiomyopathy is a clinical condition of ventricular dysfunction that occurs in the absence of coronary atherosclerosis and hypertension in patients with diabetes mellitus. It is characterized by diastolic dysfunction, which is defined as a defect in left ventricular relaxation leading to increased pressures and subsequent impaired filling during diastole. Diabetic cardiomyopathy as a clinical entity remains elusive and ambiguous. The phenomenon of diabetic cardiomyopathy is multifactorial. There are different suggested mechanisms including insulin resistance, microvascular impairment, metabolic disturbances, alterations in the renin-angiotensin-aldosterone system (RAAS) and maladaptive immune responses. Also includes oxidative stress, myocardial dysfunction, inflammation, and other mechanisms. The inflammation is frequently related to obesity and type 2 diabetes mellitus. And present to the pathogenesis of diabetic cardiomyopathy. The activation of different signalling pathways like NF-kB, c-jun NH2-terminal kinase, p38- MAPK, could moderate a state of inflammation and that is linked to insulin resistance. Diabetic cardiomyopathy is accelerated by the variation in the adaptive and innate immune systems. The stimulation of macrophage polarization to classic (M1) or alternative (M2) phenotypes and pro-inflammatory T helper cells repeatedly occurs in states of insulin resistance or obesity. Early signs and symptoms are subclinical and Patients may not have any appearance of signs or symptoms. Detection is possible with very responsive methods such as strain rate, strain, and myocardial tissue velocity. Diabetes is an unconventional contributor to left ventricular hypertrophy (LVH) and myocardial stiffness. Diabetic cardiomyopathy is characterized by interstitial fibrosis, mainly composed of collagen, and perivascular fibrosis. Regan et al found a significant increase in the deposition of collagen around the vessel and between the myofibers in heart biopsies from diabetic patients. Diabetic cardiomyopathy in humans is characterized by diastolic dysfunction, which may precede systolic dysfunction. DCM involves some stages of the disease, which include a period in which symptoms are not present, and resting left ventricular dimension and function are still normal. Left ventricular dysfunction can be characterized by exercise, and cardiac performance after exercise could be a tool to detect early contractile dysfunction in diabetes. Therefore, a detailed study of Diabetic Cardiomyopathy was done and novel therapeutic strategies can be made in future studies.

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