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"Unravelling the pathogenesis of Cardiovascular Disease in Diabetes: Molecular Mechanisms and Clinical Implications"

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ABSTRACT:
The pathophysiology of the link between diabetes and cardiovascular disease (CVD) is complex and multifactorial.various mechanisms contribute to the impairment in systolic and diastolicfunction in patients with diabetes, and there is an increased recognition that these patients develop heart failure independent of the presence of coronary artery disease or its associated risk factors.A huge pathological alternate is thickening of capillary basement membrane, boom in vessel wall matrix and mobile proliferation appearing in vascular headaches like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and peripheral vascular insufficiency.Understanding these profound mechanisms of disease can help clinicians identify and treat CVD in patients with diabetes, as well as help patients prevent these potentially devastating complications. This article reviews the biological basis of the link between diabetes and CVD, from defects in the vasculature to the cellular and molecular mechanisms specific to insulin-resistant states and hyperglycemia. It concludes with a discussion of heart failure in diabetes, a clinical entity that demonstrates many of the mechanisms discussed.

Keywords: cardio vascular diseases, diabetis mellitus, vascular mechanisms

I. INTRODUCTION:

Diabetes mellitus (DM) is a miscellaneous complaint characterized by hyperglycemia, insulin insufficiency, and or insulin resistance. It's an adding health and profitable burden throughout the world.[1] Cardiovascular complaint (CVD) is one of the leading causes of morbidity and mortality among people with diabetes. Coronary roadway complaint (CAD), supplemental vascular complaint (PVD), ischemic stroke, and heart failure are major instantiations of CVD associated with diabetes.[2] also, diabetes is frequently accompanied by synergistic threat factors similar as hypertension, rotundity, systemic inflammation, hypercoagulability, and dyslipidemia; which further increase CVD death rates.[3] There are colorful biochemical mechanisms that singly increase the threat of CVD in people with diabetes, and these will be explored in this review.[4] Further, in this review, we epitomize the pathophysiologic abnormalities which promote CVD in diabetes as well as contemporary precautionary and remedial approaches.[5]

Insulin resistance as seen in rotundity, pre-diabetes, and diabetes promotes atherosclerosis through development of vascular stiffness, hypertension, diabetic dyslipidemia, and increased systemic and vascular towel inflammation. Reduction in endothelial nitric oxide (NO) synthase and NO product along with increased product of endothelin and adhesion motes lead to endothelial cell dysfunction, vascular stiffness, and increased entry of seditious cells into the vasculature promoting shrine conformation.[6]

Primary features of diabetic cardiomyopathy include cardiac stiffness, myocardial fibrosis, and diastolic dysfunction which ultimately lead to disabled systolic function and heart failure. Insulin resistance, abnormal metabolic insulin signaling in cardiac myocytes, and hyperglycemia contribute to the development and progression of diabetic cardiomyopathy.[7]

During the original stages, diabetic cardiomyopathy is clinically silent, characterized by microstructural changes in myocytes, increased ventricular fibrosis and stiffness leading to diastolic dysfunction.[8]This is followed by accelerated myocyte apoptosis due to oxidative stress, blights in calcium transport, increased TGFβ1, and mild cardiac autonomic neuropathy ultimately performing in farther myocardial fibrosis. These abnormalities may reflect changes in left ventricular structure and hypertrophy with sensible changes in diastolic and after systolic function on echocardiography.[9]

Atherosclerosis is the major trouble to the macrovasculature for cases with and without diabetes. In addition, still, small vessels throughout

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the body are affected by diabetes, including those in the brain, heart, and supplemental vasculature. This small vessel damage is generally not related to atherosclerosis and isn't prognosticated by lipid situations. Whereas atherosclerosis is the major trouble to the macrovasculature, a variety of cellular and molecular mechanisms contribute to microvascular complaint in diabetes.[10]

Chronic heart failure is a complex clinical pattern that can affect from any structural or functional cardiac complaint that impairs the capability of the ventricle to fill with or eject blood. Heart failure in a case with diabetes may arise from myocardial damage performing from an ischemic, thrombotic event. In this case, endothelial dysfunction, oxidation and glycation of atherogenic lipids, and the hypercoagulability of the blood are major contributors to the case's performing heart failure.[11]

The "Glucose Hypothesis" In the Heart

High glucose situations over time play an independent part in the development of CVD. The " glucose thesis " linking high glucose to cellular damage is grounded on the conception that for numerous a tissues in the body and or under certain metabolic conditions, glucose transport across the cell membrane is limited by insulin and high glucose attention bombard cells with high intracellular glucose and glucose metabolites.[12]The attendant dropped insulin signaling and glucose uptake appear to be important blights along the pathophysiologic pathway to diabetic cardiomyopathy(CM). The result is abnormal intracellular calcium signaling, lowered insulin-stimulated coronary endothelial nitric oxide(NO) synthase exertion, and NO product. Added to this is an unhappy activation of the renin- angiotensin aldosterone system(RAAS) in diabetes and the activation of the maladaptive signaling pathway mTOR- S6K1 due to overnutrition. The end result of these abnormalities is cardiac stiffness and diastolic dysfunction, and over time, clinical heart failure.[13] Pathogenetic factors that are known to contribute to atherosclerosis, microangiopathy, diabetic CM, and cardiac autonomic neuropathy. a Combination of blights including disabled insulin signaling, abnormal glucose uptake (increased or dropped), generation of oxidative stress, and conformation and deposit of glycation and products.

Pathophysiology:

The underlying pathophysiology of atherosclerotic cardiovascular disease (ASCVD) in diabetes is multifactorial which now no longer most effective entails macro vascular plaque formation however additionally continual insults at numerous mobile and molecular stages because of hyperglycemia and insulin resistance.

Obesity mainly visceral weight problems which frequently precedes improvement of kind 2 diabetes (T2DM) is related to different metabolic danger elements consisting of insulin resistance, atherogenic dyslipidemia, hypertension, and a pro-thrombotic and pro-inflammatory state.[47]

Concentrations of pro-coagulant factors such as fibrinogen, protein C, and von Willebrand factor are elevated in individuals with obesity compared to lean individuals, which along with increased levels of plasminogen activator inhibitor-1 generates a prothrombotic state.[48] Additionally, multiplied manufacturing of angiotensinogen and aldosterone from an accelerated adipocyte mass turns on the renin-angiotensinaldosterone system (RAAS) and in turn, induces vascular stiffness and hypertension.[49.]

Insulin resistance as visible in obesity, pre-diabetes, and diabetes promotes atherosclerosis via improvement of vascular stiffness, hypertension, diabetic dyslipidemia, and improved systemic and vascular tissue inflammation.Reduction in endothelial nitric oxide (NO) synthase and NO manufacturing in conjunction with improved manufacturing of endothelin and adhesion molecules result in endothelial cellular dysfunction, vascular stiffness, and improved access of inflammatory cells into the vasculature selling plaque formation.[50] Hyperglycemia promotes CVD with the aid of using some of mechanisms. Elevated glucose tiers result in the activation of protein kinase C, the polyol and hexamine pathways with expanded formation of superior glycation end-merchandise which use up intracellular anti-oxidants and accumulation of radical oxygen species.[51] Excess radical oxygen species causes endothelial dysfunction via mitochondrial injury and reduced endothelial NO production.

Furthermore, a hyperglycemic environment in animal models has shown to cause increased glucose uptake in vascular smooth muscle cells leading to impaired contractility and induction of a pro-inflammatory.[52] and atherogenic vascular smooth muscle cell phenotype in response to various vascular injuries.

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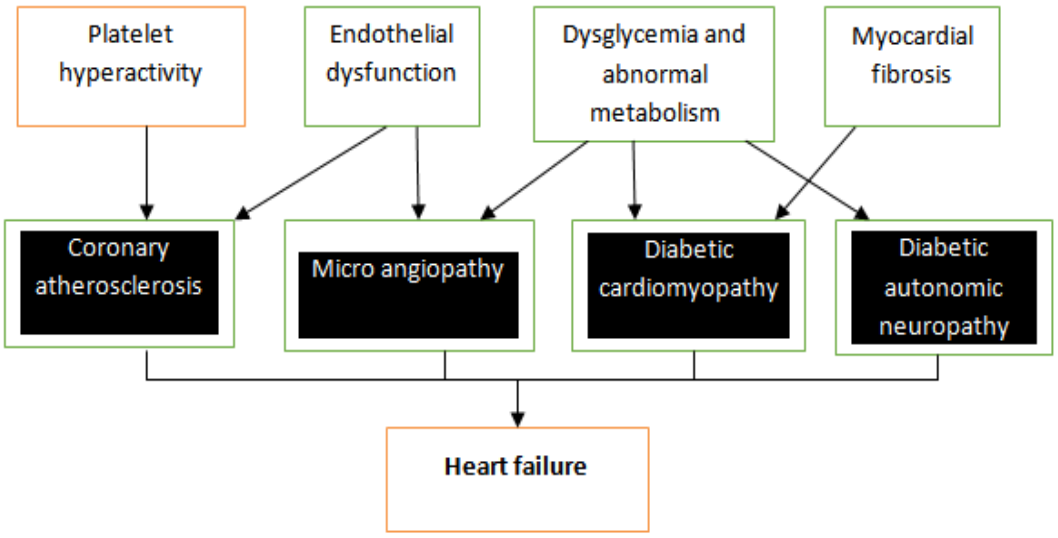

Figure 1. Represents the pathophysiology of Heart failure in Diabetes Mellitus

MACROVASCULAR COMPLICATIONS:

Angina And Ischemia

Angina pectoris risk is higher in people with diabetes (recognized ischemia). a condition that affects NIDDM and non-diabetics equally frequently.[14]In the Framingham Heart Study, between 30 and 50 percent of ischemia events are symptomless (unrecognized).[15] a condition that affects NIDDM and non-diabetics equally frequently.

Myocardial Infarction

Diabetics of all ages have higher rates of myocardial infarction (MI). MI risks areapproximately twice as high in middle-aged males and triple as high in middle-aged womencompared to non-diabetics. The effectiveness of thrombolytic therapy in diabetics may belimited by more severe coronary atherosclerosis at the time of the MI, and thrombolysis isgenerally contraindicated in the presence of proliferative retinopathy.[16]Glycemia, acidosis, and severe hypertriglyceridemia should be under control at the time of a MI infarction. Although the extent of an infarction is typically not larger in people with diabetes than it is in those without diabetes, consequences such early death, cardiogenic shock, myocardial rupture, and acute arrhythmias seem to be more common in people with diabetes.[17-20]

Angiography, Angioplasty, and Revascularization

According to pathological evidence, diabetics' CAD and myocardial lesions are more severe than those of non-diabetics',[21] and diabetics' hearts have poor capillary densities. 37 According to studies conducted in the last ten years, diabetes is linked to greater incidence of restenosis following angioplasty.[22] According to some findings, more severe diabetes and poorer glycemic control may have a negative impact on the long-term results of coronary artery bypass surgery (CABG).[23] In diabetics with myocardial ischemia and two or more major coronary artery blockages, the Bypass Angioplasty Revascularization Investigation (BARI) evaluated the benefits of CABG and percutaneous transluminal coronary angioplasty (PTCA).[24]

Congestive Heart Failure and Cardiomyopathy

Diabetic cardiomyopthy is a completely uniqueshape of coronary heartailmentcharacterisedthrough an early disorder in diastolic rest that progresses to conjective coronary heart failure withinside the absence of detectable atherosclerosis or dangerelementsinclusive of high blood pressure or dyslipidemia. Hence, in its naturalshape, diabetic cardiomyopathy does now no longerincrease from ischemia because of the coronary vasculature. The Pathophysiological elements in diabetes that pressure the improvement of cardiomyopathy encompass systemic metabolic derangement as definedwithinside the above section “opportunity

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glucose hypothesis".[26] Diabetes is an crucial precursor of CHF, the frequency turned into expanded twofold for guys with diabetes and fivefold for ladies with diabetes forty one Deterioration into congestive failure passed off specially in diabetic ladies who had skilled an MI.[27,28]Diastolic dysfunction, characterized by an increased left ventricular end diastolic pressure (LVEDP), a reduced left ventricular end diastolic volume (LVEDV), and normal ejection fraction may be more common in diabetics than in nondiabetics.

MICROVASCULAR COMPLICATIONS:

Microangiopathy And Myocardium:

Diabetic micriangiopathy is characterized by abnormal growth and leakage of small blood vessels, resulting in local edema and functional impairment of tissues. Although there are multiple mechanisms leading to the impairment of microcirculation in diabetes, the result is dysregulated vascular regeneration that impacts tissue perfusion independently from coronary arterial flow.[22]

Cardiac Autonomic Neuropathy:

One of the most frequent yet least understood consequences of diabetes is CAN. The cardiovascular, gastrointestinal, ophthalmic, and genitourinary systems are all susceptible to autonomic neuropathy. It affects the sympathetic and parasympathetic nerves in an ascending, length-dependent manner.[29]Tachycardia, orthostatic hypotension, and other symptoms are examples of manifestations. Since the vagus nerve is the largest autonomic nerve in the human body, it is frequently the first to be impacted. It is the cause of 75% of all parasympathetic activity, loss of parasympathetic tone, and insulin resistance due to an increase in norepinephrine and other stress hormones.[30]Damage to the vagal nerve causes an increase in resting heart rate and an unopposed cardiac sympathetic outflow.[31]This can cause diastolic dysfunction, left ventricular hypertrophy and cardiac remodeling in the absence of CAD.

Diabetic Retinopathy

Retinopathy resulting from diabetes Patients with type 2 diabetes may start to develop retinopathy. Retinopathy may develop as a result of diabetes through a number of pathogenic processes. Aldose reductase might contribute to the emergence of problems from diabetes. The first enzyme in the intracellular polyol pathway is aldose reductase. Glucose is converted into glucose alcohol (sorbitol) by this route. Sorbitol builds up in cells as a result of high glucose levels increasing the flow of sugar molecules via the polyol pathway. One underlying mechanism in the development of diabetic microvascular problems, such as diabetic retinopathy, has been proposed to be osmotic stress caused by sorbitol buildup.[47]

Diabetic retinopathy is typically divided into two categories: proliferative and background. To interpret eye examination findings and guide patients regarding the course and prognosis of their diseases, it is vital to have an understanding of each features.

Features of expertise retinopathy include tiny hemorrhages in the retina's middle layers. They are sometimes referred to as "dot hemorrhages" because they clinically resemble "dots." Lipid deposition, which usually happens around the bleeding edges, is the cause of hard exudates. Small vascular dilatations called microaneurysms can develop in the retina and are frequently the initial indication of retinopathy. In a clinical retinal examination, they show up as red dots. Microvascular leakage can cause retinal edema, which is a sign of a damaged blood-retinal barrier. It looks like grayish patches on the retina. Since retinal edema can occasionally be linked to vision decline, treatment may be necessary.[8]

The development of new blood vessels on the retina's surface is a symptom of proliferative retinopathy, which can result in vitreous hemorrhage. Cotton wool spots, or white patches on the retina, may indicate the onset of proliferative retinopathy. Blindness may result from vitreous hemorrhage and traction retinal detachment if proliferation persists. If nothing is done, blindness could happen. Close monitoring for the presence or advancement of retinopathy in diabetic patients is essential because laser photocoagulation can frequently stop proliferative retinopathy from leading to blindness. [8]

Diabetic Nephropathy:

The excretion of 30–299 mg of albumin every 24 hours is referred to as microalbuminuria. Microalbuminuria in diabetic patients usually develops into proteinuria and overt diabetic nephropathy if treatment is not received. Type 1 and type 2 diabetes both progress in this way. A 24-hour urine collection or a spot urine measurement of microalbumin can be used to screen for diabetic nephropathy or microalbuminuria. Spot measurements are more

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practical for patients than 24-hour urine collections, and measuring the microalbuminto-creatinine ratio may assist adjust for urine concentration or dilution. It is crucial to remember that hematuria, exertion, and urinary tract infections can all result in erroneously increased urine protein levels.[13]

As part of various diabetic problems, prevention is the first line of treatment for diabetic nephropathy. It has been proven that ACE inhibitors and ARBs can reduce the chance of microalbuminuria patients developing macroalbuminuria by as much as 60–70%. Even in individuals without hypertension, these medications are advised as the initial pharmacological treatment for microalbuminuria. 9. Similarly, managing hypertension helps people with macroalbuminuria. Controlling hypertension in diabetic kidney disease patients with macroalbuminuria reduces the glomerular filtration rate (GFR) deterioration. In addition to decreasing blood pressure, treatment with ACE inhibitors or ARBs has been demonstrated to further reduce the risk of renal disease progression. It has been showed that ACE inhibitor and ARB combination therapy provides extra renoprotective effect.[10]

Conduction Disorders, Atrial Fibrillation, Heart Rate Variability

Left bundle branch block and atrial fibrillation appear to be more common among diabetics.[32,33]Aging and diabetes are associated with a cardiac autonomic neuropathy that may be reflected by abnormalities such as increased heart rate after 15 minutes of rest, less beat-to-beat variability in the heart rhythm, and orthostatic hypotension.[34,35]According to studies, diabetics with cardiac autonomic neuropathy have a worse 5-year survival rate than a population sample that is age- and sex-matched.[36,37]

Structural and Functional Characteristics of Cardiac Dysfunction in Diabetes

Imaging research have found out left ventricular concentric transforming as a applicable function of diabetic myocardium, which can be related to impaired myocardial energetics and decreased systolic.[38,39] Hypertrophy of the diabetic coronary heart is the outcome of myocardial triglyceride deposition and/or expanded extracellular quantity as a trademark for collagen deposition and fibrosis,[40,41]With the expanded extracellular extent being predictive for mortality and coronary heart failure on this population. In addition, hyperinsulinemia because of insulin resistance is likewise concept to immediately sell myocardial hypertrophy.[42]Deposition of superior glycation ceasemerchandise constitutes a ridingelement for microvascular harm in diabetes and has been related to cardiomyocyte stiffness and myocardial collagen deposition.[43] The consequential growth in myocardial stiffness interprets to diastolic dysfunction, decreased myocardial strain, and atrial enlargement, which has been related to an multiplied occurrence of atrial traumatic inflammation in sufferers with diabetes.[44-46]

II. CONCLUSION:

Diabetes mellitus is a chronic disease with seriouslife-threatening complications. CVD remains the commonest cause of mortality and morbidity. Uncontrolled diabetes, hypertension, dyslipidemia, and obesity are some of the key predisposing risk factors in the development of CVD. More research is needed to better understand the relationship between diabetes and CVD.

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