Overview of Diabetic cardiomyopathy

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Abstract

Diabetes mellitus may be a major health problem worldwide. Till the last decade, 285 million individuals already have that common disease, and this range is expected to markedly extend to virtually 700 million individuals by the end of 2040 (1). Type two diabetes mellitus (T2DM) is considered one of the contributing risks for causing cardiac failure (2). Heart failure may be a complex disease in diabetic patients. It is caused by a rise in macrovascular and microvascular abnormalities, leading to ischemic events and a change in vascular permeability (3, 4). Atherosclerosis and high blood pressure that occur in patients with diabetes and share in causing ischemic heart disease (IHD) and peripheral arterial disease, that has a cardiac effect. However, in addition to those contributing triggers, diabetes can cause HF directly by multiple mechanisms, that are principally driven by increased blood glucose, increased insulin levels, metabolic abnormalities, and oxidative stress (5).

Keywords: diabetes mellitus, insulin resistance, SGLT-2 inhibitors, hyperglycemia, heart failure.

Diabetic cardiomyopathy is defined as abnormal cardiac muscle structure and function with the absence of any other risk factors, like, high blood pressure, coronary heart disease and valve disease in diabetic patients. It was formerly described in 1972 (6) and confirmed in 1974 Framingham Heart Study that concluded that heart failure is more in diabetic ladies (5-fold) and men (2.4-fold) on adjustment for different risk factors, like age, a coronary heart condition, and high blood pressure. (7) In 2013, ACC, AHA (8) and ESC and the European Association for the Study of Diabetes (9) outlined diabetic cardiomyopathy as a clinical condition of LV dysfunction that happens within the absence of coronary arterial disease and HTN in patients with DM. In its early stages, diabetic heart disease includes a hidden subclinical phase characterized by structural and physiological abnormalities, as well as left ventricle (LV) hypertrophy, fibrosis, and cell signal abnormalities. These changes of myocardial fibrosis and stiffness and associated subclinical diastolic dysfunction usually evolve to cardiac failure with preserved ejection fraction and ultimate systolic dysfunction then heart failure with reduced ejection fraction.

Mechanisms:

The cardiac impact of DM happens by locally numerous pathways on the microcirculation and relaxation pattern of sarcomeres & systemically by peripheral arterial disease, activation of renin-angiotensin-aldosterone system (RAAS) and autonomic dysfunction. These mechanisms are established as a result of the associated inflammatory process, endothelial dysfunction, and perfusion changes, with unbalanced oxidative stress.

High blood sugar:

Mitochondria exposed to high blood sugar causing the release of reactive O2 species resulting in dysfunction of nitric oxide synthases and bioavailability leading to reduction of intracellular cyclic guanosine monophosphate (cGMP) (10). A decreased level of intracellular protein kinase G (PKG) decreases cardiac muscle distensibility (11) as a result of the hypophosphorylation of the sarcomeric titin (12).

In humans, the same results were discovered in cardiomyocytes of persons who have aortic valve stenosis and diabetes who showed improvement in stiffness once exposed to PKG (13). Hyperglycemia additionally ends up in rising in kinase C protein (PKC) of fibroblasts, that successively increase collagen synthesis and deposition (13, 14). Hyperglycemia causes myocardial dysfunction by dextrose metabolites. β-N-acetylglucosamine that bind to a number of proteins (serine or threonine), and alter its physiology (15).

An important example is that the alteration of kinase II proteins leading to decreased myocardial systole and diastole (16). Mitochondrial proteins are at risk of modification by O-G1cNAc with impairment heart function.

Insulin resistance:

The potential risk of cardiac failure in type two diabetes is insulin resistance, especially in obese persons. The prevalence of obesity as such will increase current levels of blood sugar and FFA (free fatty acids). Additionally, insulin resistance and obesity are accountable for a constellation of signal abnormalities, resulting in a general inflammatory state that ends up in the assembly of reactive oxygen species and a reduction in nitric oxide bioavailability. Insulin insensitivity induces cardiac muscle energy imbalance by increasing the employment of less economical sources to the harm of aldohexose use, leading to decreased (ATP) synthesis (17, 18). High insulin levels, also, activate bound pathways, like PI3K/Akt, that is concerned in cardiac muscle hypertrophy. It also induces the expression of a lot of rigid molecules of the sarcomeric titin, impairing heart distensibility (19).

The inflexibility of power supply:

Diabetics with ischemic heart and people with cardiac failure might have got less glucose utilization ability in comparison with non-diabetic cardiac failure patients, in spite of having an equivalent level of glucose transporters (GLUT-4) in cardiac muscle specimens. This hypothesis suggests that insulin insensitivity would oppose the power of diabetic patients' cardiac muscle to resist ischemia and, thus, worsen CV prognosis (20).

Studies utilizing high insulin/normal glucose levels postulate that a rise in insulin secretion increases pulse, blood pressure and cardiac muscle O2 use (as evaluated by extraction of FDG -18) in diabetics and non-diabetics. The presence of insulin decreases the provision of non-esterified fatty acids and suppresses the oxidization of FFA.

However, the oxidization of FFA by the cardiac muscle is multiplied. In such cases, there's a decrease in cardiac muscle potency, probably because of the change in the energy substrate (from dextrose to FFA), since the FFA metabolism uses a larger quantity of O2 (21). In persons with diabetes, the fast and forceful decrease of FFA by drug intervention results in a fulminant decline in myocardial function, corroborating this theory. Cardiac function depending on one energy supply must be available. (22)

Lipotoxicity:

The uptake of myocardial uptake of FFA, if more than the oxidization capability of these particles resulting in the accumulation of triglycerides, heart steatosis, and death of cardiomyocytes leading to left ventricular systolic dysfunction. This method has been detected in animals and is named lipotoxicity. The amendment in the energetic substrate, caused by the decrease of insulin-mediated glucose uptake, additionally results in diastolic dysfunction (23). production of lipid intermediates, like diacid-glycerol (24), could also be noxious to microcirculation, by the result of nitric oxide synthases and reduction of cardiomyocyte distensibility, as delineate higher. Myocardial steatosis has additionally been related to diastolic dysfunction in diabetics (25).

Microvascular Rarefaction:

One of the pathophysiological mechanisms of diabetic cardiomyopathy is that the decrease of microvascular cardiac muscle perfusion and coronary flow reserve (28) caused by the action of AGEs within the microcirculation and rarefaction of capillaries and decreased luminal area/myocardial tissue ratio due to cardiac muscle cells hypertrophy (29). Capillary rarefaction decreases nitric oxide bioavailability to encompassing cardiomyocytes and causes tissue hypoxia related to the production of reactive oxygen species that ends with cell death and cardiac systolic dysfunction.

1. Deposition of the advanced glycation end product (AGEs):

AGEs are present in smooth muscle cells of the cardiac muscle n (13), and within the extracellular matrix, between myocytes (26). AGEs induce inflammation, quenching abundant of the nitric oxide made locally resulting in a decrease in microcirculation perfusion at rest, however additionally of the coronary reserve throughout flow hyperemia. Additionally, they trigger the assembly of reactive oxygen species via the NADPH oxidase enzyme, which can lead to cell death and, then myocardial dysfunction (27).

Inflammatory and autoimmune Response:

The autoimmune response occurs within the pathophysiology of diabetic cardiomyopathy with HFEFr as a result of myocardial anti-myosin autoantibodies that were known in type one diabetic patients once infarcted and non-diabetic patients with autoimmune myocardial inflammation. Generally, diabetic patients, release troponins that are associated with heart failure with reduced ejection fraction and cardiomegaly. (30)

Autonomic neuropathy:

Altered glucose metabolism and associated insulin resistance increase sympathetic activity that's associated with hypertrophy and fibrosis of cardiac muscle (31). Overtime, cardiac sympathetic denervation occurs, an incontrovertible event that disrupts the β-adrenergic signal and decreases cardiac muscle contraction and relaxation. (32, 33).

Upregulation of Renin-angiotensin-aldosterone system (RAAS):

The cardiac muscle of diabetic patients additionally presents RAAS and local endothelin upregulation (34). (35) It has many other functions, such as weight reduction, blood pressure reduction, appetite reduction & decrease gastric emptying. It is rapidly inactivated by (DPP-4). So, it acts in a physiological manner (activates insulin secretion only on the rise of blood glucose) i.e rarely cause hypoglycemia.(36)

New oral hypoglycemic:

GLP-1 Antagonists:

(GLP-1) is a hormone secreted in GIT after meals, increases insulin secretion, thereby decreases the postprandial rise in blood glucose.

DPP-4 antagonists: DPP-4 is present in many cells that reactive against GLP-1. It is only active in glucose metabolism; it also has pleiotropic effects (anti-inflammatory, endothelial function and cell survival). (37)

DPP-4 activity has a relation to human and animal heart dysfunction. (38)

SGLT-2 antagonists:

They have many cardiovascular benefits (they decrease cardiovascular mortality, non-fatal CVS and myocardial infarction by 14%, and decrease hospitalization for heart failure by 35% (39)

Because of those benefits, many trials for their use in non-diabetic patients with heart failure are planned. (40).

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