Insight into the Pathogenesis, Diagnosis, and Current Strategies of Diabetic Cardiomyopathy

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Abstract. The concept of diabetes cardiomyopathy (DCM) was first introduced by rubler and his colleagues. DCM refers to the adverse myocardial structure which is associate with diabetes. The primary pathogenesis of diabetes mellitus, insulin resistance, is also a predisposing factor for cardiovascular disease. In addition, diabetic disease is also associated with abnormal cytosolic calcium regulation, systolic dysfunction, cardiac remodeling, myocardial stiffness, and hypertrophy. Diabetic patients are normally affected by cardiovascular disorders. Several diagnosis approaches could be used in DCM, including echocardiography, magnetic resonance imaging (MRI) and nuclear imaging. Given the broad influence and complex mechanism of DCM, effective therapies are urgently needed. Current treatments for DCM are mainly target several critical proteins. Lifestyle interventions for patients with DCM are beneficial as well. DCM has been known by researchers for 50 years, but the relevant signaling pathways and targeted therapies still need further investigation.

Keywords: Insulin, Diabetic Cardiomyopathy, Type 1 Diabetes.

1. Introduction

The concept of DCM was first introduced in 1972 when Rulber et al observed four patients with diabetic glomerulosclerosis who developed congestive heart failure and arrhythmias without relevant valvular disorder and alcohol abuse [1].

There is a significant health problem associated with diabetes throughout the world. Cardiovascular disease is one of the most common case fatality risks in diabetes cases (about 50%). Compared with non-diabetes patients, the prevalence of heart failure in diabetes patients increased 6-8 times, and the prognosis was poor. Diabetes mellitus refer to a series of metabolic disorders which are associated with the high glucose. Furthermore, the dysregulated insulin mainly leads to the hyperglycemia.

This paper looks into diabetic cardiomyopathy mechanism, its clinical manifestations, diagnoses and treatments from different perspectives. Generally, DCM mechanism include the following three classes: a) insulin resistance; b) abnormal cytosolic calcium regulation; c) systolic dysfunction. Diabetes patients with unbalanced blood glucose levels are potential to get a range of complications, with diabetic heart disease being one of the most severe complications and leading to the most death in diabetes patients. When the patient's body's sugar and fat metabolism is not effectively controlled over a long period, it can lead to abnormalities in the several tissues of the heart. In order to prolong the survival of the patient, it is essential to treat the symptoms as soon as they appear.

At present, there are plenty of research has been done on the topic of diabetic cardiomyopathy, clinical manifestation has been widely collected for study. Despite the number of efforts and resources invested to study the disease, due to its complex nature, it is still difficult to set a clear standard of diagnose clinically and distinguish DCM clearly from other diseases that are having similar symptoms such as hypertension and other asymptotic cardiac diseases. Still, this paper identified several diagnostic methods have been developed and targeted to help patients of different stages alleviate

illness and pains. At last, current therapies are explored in this paper and broadly have been categorized into two classes of medical treatment using Glucose-lowing therapies and non-medical treatment using lifestyle intervention methods [2].

2. DCM pathogenesis

2.1. Insulin resistance

Insulin resistance is characterized by a decline in the capacity of insulin to promote glucose uptake and utilization, a reduction in glycogen synthesis, and a corresponding decline in the capacity of insulin to inhibit lipid oxidation. in this situation, the human body would secrete more insulin, which could make the situation worse. Diabetes is primarily caused by insulin resistance, which is also one of the major risk factors for cardiovascular disease. The principal causes of death for diabetic patients are cardiovascular and brain conditions.

Insulin resistance causes hyperglycemia, which results from downregulated glucose capture by muscle and increased gluconeogenesis in liver [3]. Due to the patient's body's disordered glucose transport system, improper glucose metabolism through certain auxiliary metabolic pathways is brought on by intracellular glucose build up and undesirable glucose metabolites. For instance, decreased interaction between polyol as well as protease results in aberrant oxidative radical production and increased advanced glycation end products (AGEs). AGE precipitation worsens heart fibrosis and causes diastolic dysfunction.

In addition to this, hyperglycemia caused by insulin resistance accelerates atherosclerosis. Mainly because the synergy between oxidative stress and systemic inflammation can damage the endothelium cells of the arteries and develop the overactivated immune response within the arterial lining. This is initially elicited on by an overabundance of pro-inflammatory macrophages in the patient's body, which is followed by lipids and oxidized lipoprotein accumulation in the intima, and plaque formation. Over time, blood flow in the body is impaired and blood clots form as the plaque ruptures, eventually leading to a myocardial infarction [3].

Furthermore, free fatty acids (FFAs) are vital energy-supplying substances for the heart because of their low oxidation efficiency, therefore they have greater energy input. When insulin resistance occurs, insulin excess increases due to the downregulation of CD36 protein, which promotes increased cardiac uptake of FFAs. When the heart is subjected to additional stress, adverse metabolic reactions may occur, lowering fatty acid use and promoting lipid deposition within the cardiac muscle. This deposition affects apoptosis, cardiac hypertrophy, and contractile dysfunction [3].

2.2. Abnormal cytosolic calcium regulation

The fine regulation of calcium homeostasis in cardiomyocytes is critical to ensure cardiac contractile function. Abnormal L-type $Ca2^{+}$ channel (LTCC) function caused by diabetes, upregulated sarcoplasmic reticulum (SR) $Ca2^{+}$ leakage due to the gain-of-function mutation of ryanodine Receptor 2 (RyR2) channel gene and insufficient SR $Ca2^{+}$ uptake in type 1 sodium–calcium exchanger different from those in T2D can induce arrhythmias and ultimately systolic dysfunction [4].

Among them, oxidative stress brought on by mitochondrial malfunction enhances SR $Ca2^{+}$ leaking through oxidative RyR2 channels., promoting ventricular translocation [4]. In addition, the imbalance of calcium homeostasis in diabetic cardiomyocytes is mainly related to the altered activity of SR $Ca2^{+}$-ATPase (SERCA2a) and its inhibitor phosphoprotein (PLB) [4]. Increased PLB mRNA expression, decreased SERCA2a activity, and decreased sarcoplasmic reticulum reuptake of $Ca2^{+}$ lead to cytoplasmic calcium overload, impaired relaxation, and myocardial diastolic dysfunction.

2.3. Systolic dysfunction

Without additional risk factors for heart disorders, diabetic cardiomyopathy is defined by impaired cardiac function. According to studies, patients with T2D have a heart failure occurrence which is

2.4% and 5.1% greater, respectively, than the general population. Diabetes is typified by myocardial fibrosis, diastolic dysfunction, and systolic dysfunction, correspondingly, having heart defect rates of 14.5% and 35.0% [4].

There are two major regulators in the human body: matrix metalloproteinases (MMPs) and metalloproteinases (TIMPs). They are critical to control fibroblasts and synthesize trace amounts of collagen to maintain the induced extracellular matrix stability. However, in diabetic patients, advanced glycosylation end products (AGEs) are formed from exposed proteins and lipids due to high levels of the cross-link ECM proteins, glucose. This phenomenon results in reduced ECM degradation by MMPs and increased cardiac stiffness, leading to early diastolic dysfunction. Simultaneously, myofibroblasts are differentiated by fibroblasts which also caused by AGEs. Myofibroblasts secrete excess fibrinogen and matrix proteins, destabilizing the ECM. The generation of other fibrosis-promoting agents including tumor necrosis factor (TNF) and transforming growth factor beta (TGF-β) might also result from disordered cardiac homeostasis. It might lead in improper protein precipitation in the ECM, which would compromise myocardial contractility and result in late systolic function. Furthermore, the increase of angiotensin II caused by hyperlipidemia and hyperglycemia can stimulate the accumulation of inflammatory cytokines which secreted by macrophages and lymphocytes at the damaged site, which also leads to cardiac hypertrophy and ECM changes.

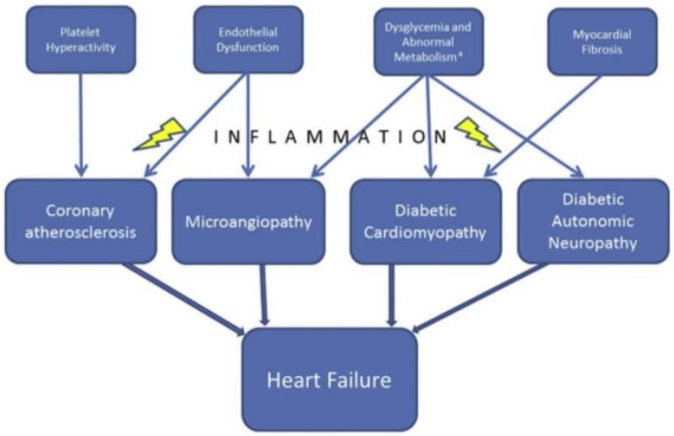

Figure 1. Pathogenesis in diabetic cardiomyopathy [5]. The current causes of heart failure are listed.

3. Clinical manifestation and diagnosis

3.1. Clinical manifestation in different stages

For healthy heart, the resting left ventricular filling is mostly passive and only about 10% of ventricular filling is caused by left atrial contractions. However, abnormalities in diastolic filling related T2D would result in a decline in ventricular wall compliance and impairment of the left ventricle's passive filling phase. With the progression of DCM, different clinical manifestations and pathophysiological performances occur in the different stages which mainly include three stages.

The first stage of DCM is usually asymptomatic. Myocardial structure and systolic function do not have substantial changes in spite of metabolic disturbances like insulin resistance. However, there are still some pathophysiological changes. Myocardial interstitium is the first area which has obvious changes. The earlier clinical manifestations include increased cardiac stiffness and decreased myocardial relaxation9 which could be identified through echocardiography, as well as a dropping of early diastolic filling and an increasing of atrial filling occur initially. Also, impaired insulin signaling would cause a reduction in myocardial blood-flow reserve.

Left ventricular hypertrophy (LVH) and cardiac remodeling are the clinical manifestations of DCM in the second stage. An elevated left ventricular mass indicates LVH which is common for both diabetes and cardiovascular disease. The number of T2D patients who have symptomless left ventricular disfunction even accounts for 50% of all, before the development of symptomatic heart failure. Advancing cardiac diastolic dysfunction is also clinical manifestations during this stage, coupled with reduced cardiac compliance. These two clinical outcomes may coexist with systolic dysfunction, leading to more symptoms such as reduced ejection fraction and an enlarged left ventricular chamber. Besides, cardiac fibrosis will increase due to a variety of changes at the cellular level in the advanced stage [6]. This pathophysiological feature would be followed by changes of diastolic function and systolic function which shown in the figure 2.

During the later stage of DCM, the most significant changes compared with the second stage are often associated with additional severities, including alterations in metabolism and the development of fibrosis. Also, the heart structure undergoes more severe changes including necrosis of the cardiomyocytes, collagen buildup and others. These all impair both systolic function and diastolic function to some extent. The incapacity of the myocardial to expel enough blood is referred to as systolic dysfunction. Compared to diastolic dysfunction which usually occurs in the earlier phases, abnormal systolic function is less common and only occurs in a few patients in the advanced stage of DCM. Eventually, heart failure is the clinical syndrome led by a complex interaction of many mechanisms after developing asymptomatic diastolic and systolic dysfunction. Long-term diabetes causes structure and function changes in the myocardium as well as insulin resistance and abnormal myocardial metabolism, all of which contribute significantly to the emergence and progression of heart failure.

3.2. Diagnosis

DCM is a disease which develops in diabetic patients irrespective of hypertension and coronary artery disease, affecting about 12% diabetic patients. However, it is difficult to have a clear standard of diagnose for DCM clinically. As many diabetic patients also have hypertension and other asymptotic cardiac diseases which would cause similar symptoms. In addition, detection of diastolic dysfunction for these patients can be influenced significantly by age. So for every age, the symptom standard needs to be modified differently. Besides, many symptoms may vary by sex. Blood test and chest X-ray are most common measurements for DCM, while there are many other distinct methods and techniques for diagnosing as well (Figure 2).

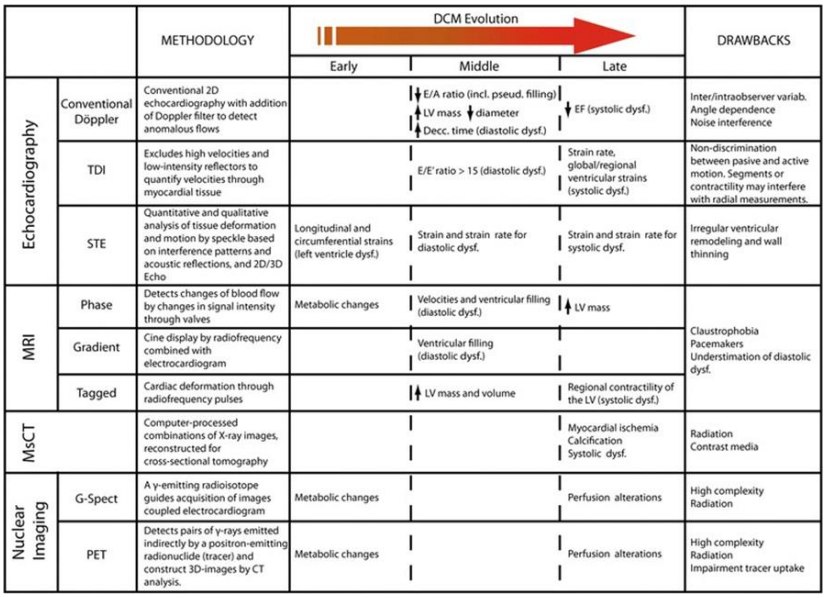

Figure 2. Main imaging approaches for diagnosis of DCM [6]. The imaging approaches mainly include echocardiography, MRI, and nuclear imaging. With the progression of DCM, different methodologies are used for early, middle, and late stages.

Echocardiography is a typical diagnostic approach for the disease. This non-invasive approach is preferred to diagnose diastolic dysfunction and has been regarded as the gold standard tool to identify heart structure abnormalities, like impaired diastolic filling [6]. Additionally, echocardiography has many modalities to use, including two-dimensional conventional doppler-echocardiography, tissue doppler imaging (TDI) and speckle tracking echocardiography (STE). Among them, conventional doppler-echocardiography can examine cardiac structure as well as detect anomalous flows because it depends on the change in frequency of ultrasound signals reflected from moving objects. Besides, TDI is typically used to measure motion during cardiac cycle and to analyze strain rate as well as general and local ventricular strains [6].

MRI is also a helpful non-invasive approach, and it emerged as a well-accepted imaging tool to diagnose functional and structural myocardial disorders. MRI produces cross-sectional images of internal structure by using strong magnetic fields and radio wave pulses. Comparing with echocardiography, MRI has higher resolution to analyze chamber size and cardiac mass distribution. Additional details of myocardial fibrosis and subclinical ischemia which are early indicators of cardiac dysfunction, can be provided by this tool. Furthermore, this approach can better characterize regional and partly systolic contractility by gradient-echo-MRI and phase-contrast-MRI. But it still has some drawbacks such as low sensitivity. And there are some safety concerns before having an MRI scan because magnet may lead to malfunction and overheat of pacemakers and other medical devices.

Two main nuclear imaging modalities are gated- single-photon emission computerized tomography (G-SPECT) and positron emission tomography (PET). Although they have a relatively low spatial resolution, they have a great sensitivity range (femto-to picomolar concentration range). γ photon emitters are common SPECT radionuclides. Using labelled myocardial perfusion agents, G-SPECT concurrently assesses heart perfusion and left ventricular function. Also, it provides 3D information about ventricular function and others. Besides, another nuclear imaging modality, PET, is considered as important tool for diagnosing DCM. It is especially used for patients who have significant left ventricular disfunction and coronary artery disease when G-SPECT cannot be used in this situation. Also, the use of positron emitters with shorter half-lives and neutron-deficient nuclides in PET makes it significantly different from SPECT. And this offers a number of benefits for PET, such as imaging a variety of functional cellular processes.

4. Current therapies

4.1. GLP-1 agonists

The glucagon-like peptide-1 (GLP-1) promotes insulin production through the incretin effect following an oral glucose load. Diabetes may cause the insulin production and utilization system to deteriorate or even stop working altogether, while administering pharmacological dosages of GLP-1 can restore insulin excretion.

This form of diabetes treatment includes the capacity to delay stomach emptying and the ability to stop pancreatic alpha cells from generating glucagon when blood sugar levels are promoted. In addition, GLP-1 receptor agonists can lower apoptosis and boost pancreatic beta-cell proliferation at the same time. When it comes to cardiovascular effects, GLP-1 agonists can increase left ventricular ejection fraction, coronary blood flow, myocardial contractility, and endothelial function while decreasing the number of infarctions and overall risks for cardiovascular events. GLP-1 also has the ability to enhance skeletal muscle glucose uptake, lessen hepatic glucose production, promote neuroprotection, and heighten satiety due to its direct actions on the hypothalamus [7].

However, the most typical side effects of GLP-1 agonists are diarrhea, nausea, and vomiting, which can result in acute kidney injury from volume contraction. Additionally, possible side effects include minor tachycardia, headaches, dyspepsia, and infections. While this family of drugs increases satiety, patients should be made aware that taking the drugs after meal may induce mild, transient nausea. The dosage of these medications should be progressively raised to avoid nausea occurs.

4.2. DDP-4 Inhibitors

Dipeptidyl peptidase 4 (DPP-4), an enzyme that is inhibited by DPP-4 inhibitors, breaks down incretin hormones. A class of hormones known as incretins is released throughout the day, and their concentrations increase during meals. The DDP-4 inhibitors can prompt insulin production and help to degrade extra glucose produced by liver [8]. As a result, the body blood glucose level could be significantly downregulated as shown in figure 3.

The activities of the stomach and intestines are downregulated as a result of the elevated amounts of incretins, which will also result in a slight decrease in appetite and a quicker feeling of fullness after eating. Mild weight loss could result from this, which is normally beneficial for those with diabetes.

DPP-4 inhibitors reduce the signs and symptoms of high blood sugar levels, including feeling thirsty and urinating a lot. Long-term control of blood glucose level lowers the risk of diseases related to multiple organs, such as feet, kidneys, and eyes.

DPP-4 inhibitors typically don't cause many other adverse effects in users. However, some individuals may develop headaches and change in bowel habits, such as diarrhea or constipation.

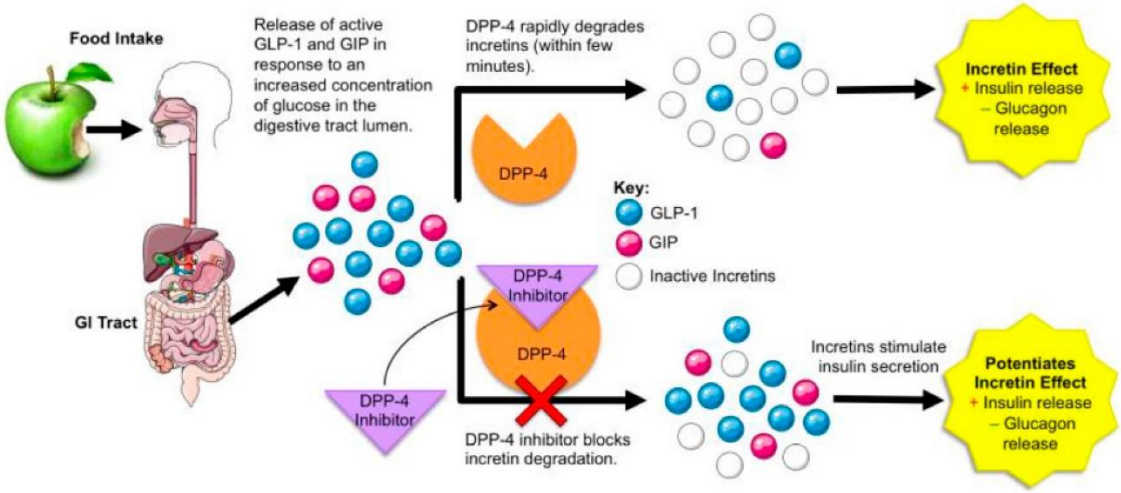

Figure 3. DDP-4 inhibitor function and mechanism of action [9].

4.3. SGLT2 inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors play a role in downregulating excessive blood glucose levels in diabetes.

SGLT-2 inhibitors function by blocking the interacted target proteins in the kidney, which are in charge of reabsorbing glucose into the blood. SGLT-2 inhibitors have also been shown to aid in accelerating weight loss and lowering blood pressure [10].

The inhibitors also improve the course of cardiovascular illnesses including ischemic heart disease, arrhythmias, and heart failure. Additionally, SGLT-2 inhibitors are linked to decreased cardiovascular and overall mortality [10].

One of the most frequent side effects of SGLT2 inhibitors is a sudden urge to urinate, along with genital yeast infections and flu-like symptoms. The U.S. Food and Drug Administration also lists other uncommon but serious problems such as amputations, kidney damage, and ketoacidosis.

4.4. Lifestyle intervention

Searching for appropriate diet for DCM patients is essential as it directly affects the control of blood sugar level.

Low sugar diets are suggested for patients. They can consume more vegetables, fruits as well as some high-fiber food, which can promote the body's sugar metabolism, lower blood sugar levels and achieve the purpose of health at the same time. Wax gourd, green pepper, corn, bean products are recommended. Eating more vitamin rich food is also beneficial. vitamin C and vitamin B contained

food, such as milk, cabbage, fish, jujube, can effectively slow down the occurrence of diabetes complications.

Foods containing calcium and selenium are also supposed to be included in the patients' diet. It is because that calcium deficiency can lead to aggravation of diabetes, while selenium is functional in regulating glucose metabolism. So diabetic patients should take more calcium and selenium contained food, such as shrimp, seaweed, sesame and garlic.

Besides, patients with diabetic cardiomyopathy should not eat a high-sugar diet and should strictly avoid smoking and alcohol.

And they are also supposed to ensure adequate sleep and avoid respiratory tract infection.

5. Conclusions

The cardiac structural and functional abnormalities associated with diabetes are called DCM. This paper looks into diabetic cardiomyopathy mechanism, its clinical manifestations, diagnoses and treatments from different perspectives.

Although this disease has been known by researchers for 50 years, its signaling pathway and targeted therapy still need further research. The crosstalk between the relevant responses and the complex pathogenesis of diabetic cardiomyopathy poses difficulties in finding effective strategies for treating diabetic cardiomyopathy. Ischemia, angina pectoris, myocardial infarction, stroke, sudden cardiac death and other diseases caused by atherosclerosis account for a considerable proportion. Therefore, prevention of cardiovascular complications is one of the critical objectives of the comprehensive management of diabetes.

Although some drugs have been shown to reduce the cardiovascular risk associated with diabetes, lowering blood glucose alone is often not enough to prevent the development of diabetic cardiomyopathy. Several signaling pathways are closely connected to the complex pathogenesis of diabetic cardiomyopathy, making it difficult to identify effective treatments for diabetic cardiomyopathy. Recent studies have evaluated the use of the renin-angiotensin-aldosterone system (RAAS) inhibitors and antagonists to treat apoptosis and myocardial fibrosis in diabetic cardiomyopathy, but the results have not been satisfactory. Diabetic cardiomyopathy can be improved by understanding the pathogenesis of the disease and identifying new therapeutic targets. Therefore, we still need a treatment plan to address the underlying causes of diabetes. One potential therapeutic route for diabetes-induced heart failure is adeno-associated virus (AAV) gene therapy, which has been shown to have great functionality in various disease settings. AAV gene therapy can target specific cells or tissues with a low host immune response. To get the virus to target the heart, we must consider various factors, including AAV serotype, promoter, etc. The Calcium Upregulation in Percutaneous Cardiac Disease gene therapy trial (CUPID) was the first approved human study of AAV therapy. The results of both the phase 1 and 2 clinical trials were favorable, with no or few side effects in some patient groups. However, its phase 2b clinical trial showed no significant improvement in disease recurrence and final events (death). Optimistically, a clinical trial using adenylyl cyclase-6 gene therapy for heart failure showed promising results and a phase 3 clinical trial is planned. AAV gene therapy is also in phase 1 trials. These studies highlight that therapeutic gene approaches are being used in the treatment of heart-related conditions and, at least in the pre-clinical phase, have been shown to offer clear promise.

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