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Overview about Correlation between Heart Failure and Diabetes Mellitus: Review Article

Azeezah Rabeea Raghib Mabrouk, Laila Mohamad Elmaghawry, Ahmed Shawky Shereef, Mohamed Saad El-Shetry
Department of Cardiology, Faculty of Medicine, Zagazig University, Zagazig, Egypt
***Corresponding author:** Azeezah Rabeea Raghib Mabrouk, **Mobile:** (+20) 01228385454, **E-Mail:** zozo.ly2017@gmail.com

ABSTRACT

Background: Myocardial shape and function can be altered by diabetes alone, without the presence of other risk factors like hypertension, ischemic heart disease and a condition known as diabetic cardiomyopathy (DCM). Diabetes is associated with a wide range of metabolic disturbances, some of which have been linked to the emergence of DCM. Some examples are elevated blood sugar levels, abnormal lipid profiles, an increase in the release of free fatty acids (FFAs), and insulin resistance.

Objective: Review of literature about correlation between heart failure and diabetes mellitus.

Methods: Heart failure and diabetes mellitus were searched for on Science Direct, Google Scholar, and PubMed. The authors also reviewed the relevant literature, nonetheless, only the most recent or exhaustive analysis was included, covering the time span from September 2010 to November 2022. There are no translation resources available, thus non-English documents are out. Unpublished articles, oral presentations, conference abstracts, and dissertations were not included because they were not considered to be part of major scientific projects.

Conclusion: There is a lack of understanding of the molecular underpinnings and pathophysiology of heart failure in diabetic people. The incidence, prevalence, and outlook for heart failure in diabetic individuals have been proven by certain clinical and epidemiologic data. In recent decades, diabetic heart disease has emerged as a major contributor to the mortality rate among diabetics.

Keywords: Heart failure, Diabetic cardiomyopathy, Diabetes mellitus.

INTRODUCTION

"Diabetic cardiomyopathy" is utilized despite its fuzziness when cardiac dysfunction is apparent in diabetic persons who do not suffer from heart disease, valve disease, or other related complications [(1)]. The term "diabetic cardiomyopathy" was coined in 1972 to describe myocardial dysfunction in diabetic individuals who did not also have valvular heart disease, hypertrophy or coronary artery disease. Diabetes-related heart failure is a poorly understood aetiology and molecular processes. Diabetes-related heart failure has been studied clinically and epidemiologically, and its incidence, prevalence, and prognosis have been documented. In recent decades, diabetic heart disease has emerged as a major contributor to the mortality rate among diabetics. Diabetic cardiomyopathy (DCM) refers to alterations in myocardial shape and function caused by diabetes alone, rather than by additional risk factors such as ischemic heart disease or hypertension. Heart energy metabolism, cardiac remodeling, and hypertrophy, and diastolic dysfunction are all symptoms [(2)].

Diabetes is associated with a wide range of metabolic disturbances, some of which have been linked to the emergence of DCM. There is an increase in the release of free fatty acids (FFAs), hyperglycemia, and insulin resistance. Hyperglycemia is a consequence of both impaired glucose utilization and elevated hepatic glucose synthesis in diabetes mellitus**.** Animal models of diabetes have provided mounting evidence that hyperglycemia is a key pathogenic mechanism in DCM. Persistently elevated blood sugar levels, however, cause metabolic and molecular alterations in cardiac cells that ultimately lead to the production of various mediators and cellular damage**.** Protein kinase C is activated, protein glycation is permanent, and the hexosamine and polyol pathways also experience enhanced flux [(3)]**.**

As a result, mitochondrial reactive oxygen species (ROS) production, glutathione reductase (GR) activity decrease, and advanced glycation end-product creation follow from these metabolic alterations. The increased oxidative stress causes a disruption in the oxidative equilibrium, which in turn damages deoxyribonucleic acid (DNA) and hastens the death of cardiomyocytes. Diastolic dysfunction can also result from hyperglycemia's direct effects on calcium (Ca^{2+}) homeostasis components**.** Diabetic hearts have reduced glucose uptake via insulin-dependent glucose transporter, resulting in decreased glucose availability in the myocardium [(4)]**.**

Increased glycation of several circulating proteins, including haemoglobin, is another consequence of prolonged hyperglycemia. Several studies have shown that cardiovascular illness such as heart attack, stroke, and heart failure are associated with elevated levels of glycosylated hemoglobin**. Perumal and colleagues [(5)]** found that diastolic dysfunction was significantly correlated with the level of HBA1c of diabetic cases**.** Chronic dyslipidemia, defined as both quantitative and qualitative abnormalities of lipoproteins, has been recently identified as a substantial contributor to the aetiology of cardiovascular disease among diabetics.

Al-Rasheed *et al.* [(6)] has demonstrated a strong correlation between elevated blood levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein (LDL-C), and lower HDL-C in diabetic rats. The myocardium's structure and function are drastically

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altered by chronic hyperglycemia. Several reports have shown that high blood sugar levels can cause heart problems in both humans and animals**.**

Hyperglycemia can cause metabolic changes that may lead to cardiac fibrosis, myocardial steatosis, and an increase in LV mass and hypertrophy. These structural changes cause cardiac dysfunction, initially manifesting as reduced diastolic function and progressing to altered systolic function, symptomatic heart failure, and LV dilatation in later stages of the illness [(7)]**.**

Liu and colleagues [(8)] showed that rats who had type 2 daibetes displayed LV dysfunction, with enlarged systolic and diastolic LV dimensions and a concomitantly smaller ejection percentage and fractional shortening of the LV. A variety of molecular mechanisms, including but not limited to elevated levels of advanced glycation end products, elevated reactive oxygen species (ROS) generation, mitochondrial dysfunction, oxidative stress, inflammation, and cell death, have been postulated to contribute to the development of DCM**.**

Heart failure and DM epidemiology:

Heart failure prevalence in connection to metabolic syndrome was assessed in a large community-based cohort experiment that followed 6814 individuals for 4 years who did not have coronary vascular disease at baseline. Two-thirds of those with metabolic syndrome also developed heart failure with reduced ejection fraction (HFrEF). Prediabetic patients are at a lower risk of developing heart failure than diabetic patients (Figure 1) [(9)].

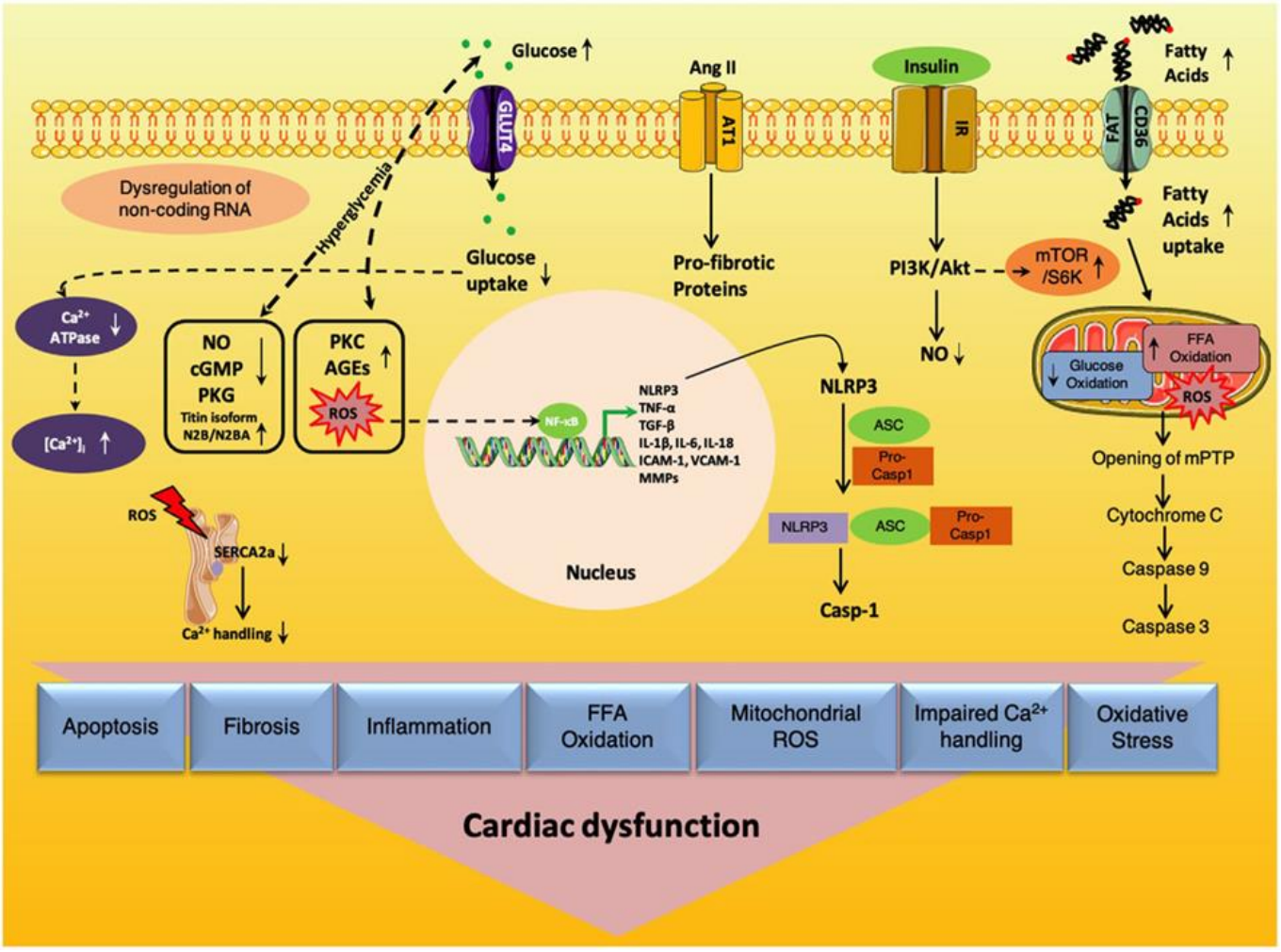

Figure (1): Cardiac dysfunction molecular mechanisms among diabetics [(9)].

Using the Kaiser Permanente Northwest database, researchers compared the long-term health and survival of people with diabetes who did not have HF at baseline to those without diabetes in a retrospective cohort analysis included 8231 individuals. Individuals with diabetes had a 30.9% increase over those without the condition in the rate of heart failure cases per 1000 individuals [10].

Similarly, the **van Melle *et al.*** [11] study from 2010 found that the probability of event heart failure was twice in people with diabetes compared to people without diabetes in 839 cases where there were no indications of heart failure at baseline despite stable coronary artery disease. A lack of studies distinguishing between HFrEF and HFpEF is regrettable. Patients with heart failure are disproportionately affected by prediabetes and diabetes, both of which are substantial predictors of mortality. More than a third of persons hospitalized for heart failure who had never been diagnosed with diabetes had impaired fasting glucose or impaired glucose tolerance, according to the study's authors.

The Long-Term outcome of diabetic patients with confirmed heart failure:

Mortality and heart failure hospitalization are the two most important clinical endpoints for determining the prognosis of heart failure patients, and the risk for both is significantly higher in diabetics [1]. One-year death estimates were 31%, significantly higher than in participants without diabetes, and by the third year, half of all diabetic individuals who had heart failure were already died [12]. The mortality rate was consistently greater among people with diabetes, according to the research. The CHARM study examined and treated patients with both diminished ejection fraction and intact ejection fraction heart failure [1].

Treatment for Diabetic Heart Failure:

Recent recommendations from both the European and American cardiology organisations do not advocate any specific treatments for patients with diabetes. Left ventricular ejection fraction (LVEF) is not the only factor that affects the prognosis of people with symptomatic HFrEF; several research, including some cluster analyses, have revealed this to be the case. As a result, high-risk individuals with diabetes require more customized treatment regimens for heart failure [13].

Prevention of heart failure in diabetic patient:

Metabolic therapies that attempt to enhance glucose metabolism may have a favourable effect on cardiac function because of the correlation between cardiac dysfunction, cardiac energy reserve, and steatosis. Nevertheless, there is no consensus on the best way to treat people who have both diabetes and heart failure, and few glucose-lowering drugs have been tested specifically in people with HF [13].

Treatment of DM in heart failure:

Metformin: Cases who had diabetes are typically started on metformin, an oral glucose-lowering medication. For a long time, doctors avoided administering metformin to heart failure patients due to the small but real risk of lactic acidosis or renal affection. In observational studies, the use of metformin has been related to a decreased mortality rate among heart failure patients. As a result, patients with serious cardiac abnormalities should be properly watched. According to the 2016 ESC recommendations, metformin is currently the therapy of choice for people with heart failure since it is both safe and effective. Patients with mild to moderate kidney dysfunction, can take metformin according to FDA recommendations of 2016. However, patients with severe kidney dysfunction should not take metformin [1].

Using a meta-analysis of 17 observational studies, researchers compared metformin-containing and metformin-free treatment regimens for patients with diabetes who also had moderate impairment in renal function, either congestive heart failure, or chronic liver disease. Cases who had chronic renal disease or congestive heart failure were less likely to be readmitted to the hospital after taking metformin, and its usage was related with a reduction in all-cause mortality across all three patient categories. Despite this, a meta-analysis of randomised metformin intervention studies has not shown a decrease in heart failure events [14].

Sulfonylureas/Insulin:

Sulfonylureas and the progression of heart failure are poorly understood. Heart failure rates did not change between sulfonylureas or insulin therapy and dietary modification in a 2015 UKPDS analysis of 3867 people who had just been diagnosed with diabetes [15]. Over the length of the study's mean follow-up time of 5.3 years, researchers did not find a statistically significant difference in the primary endpoint of mortality, MI, or stroke between the two therapy groups. Furthermore, persons with preexisting heart failure were not at a higher risk for experiencing a heart failure episode than those without heart failure [16].

Insulin therapy may worsen the prognosis for patients with diabetes and heart failure, according to other retrospective studies. On the other hand, researchers conducting the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) experiment found no association between the two. About 30 units of insulin (0.31 to 0.40 units/kg) per day were needed in that study of 12,537 patients with impaired fasting glucose, impaired glucose tolerance, or T2DM to achieve the target fasting blood glucose level of 95 mg/dL (5.3 mmol/L) [17].

The effects of higher insulin doses once metformin therapy had already been established were investigated in a cohort trial involving 6072 people. Cardiovascular mortality was higher among those who needed 100 or more units of insulin per day compared to those who needed 25 units or less (HR 2.65; 95% CI, 1.65-4.25). Higher insulin dosages were not linked to an increased risk of heart failure. High insulin dosage was associated with an increased risk of death from cardiovascular disease, although this connection was attenuated after

controlling for time-dependent factors such as haemoglobin A1c, body mass index, and hypoglycemic/cardiovascular events [18].

Thiazolidinediones:

There is evidence that thiazolidinediones (glitazones) enhance the risk of heart failure through causing fluid retention. Patients experiencing symptoms of heart failure should not take thiazolidinediones, and those with established NYHA III/IV heart failure should not begin medication [19].

DPP-4 Inhibitors:

Clinical studies for DPP-4 inhibitors were planned with the new FDA Agency standards for cardiovascular safety in mind. A risk ratio of 1.3 for major adverse cardiovascular events over placebo in a randomised controlled study is considered safe enough for commercialization in terms of cardiovascular risk. Trials are often planned to achieve glycemic equivalence between the medicine and placebo groups, therefore the reduction of HbA1c is not necessary for a treatment to be effective. Therefore, subjects who get the placebo have a greater incentive to alter their preexisting diabetic medications [1].

Although no medicine studied improved diabetes outcomes above those seen with placebo when added to standard care, cardiovascular safety in high-risk populations was proven. Hospitalizations for heart failure were the secondary endpoint in SAVOR-TIMI 53, and saxagliptin surprisingly increased the number of these occurrences [20].

The absence of a class effect is suggested by these findings and will be confirmed by future research including DPP-4 inhibitors. DPP-4 inhibitors and other glucose-lowering therapies were related with decreased cardiac and all-cause mortality in a retrospective, propensity score-matched examination of patients with heart failure and diabetes [21].

Patients who were newly prescribed DPP-4 inhibitors like sitagliptin fared better in a large retrospective analysis compared to those who were prescribed pioglitazone, sulfonylureas, or insulin. In a retrospective cohort study encompassing 1,499,650 adults with diabetes and 79,800 with a history of heart failure, DPP-4 inhibitors and GLP-1 receptor agonists (GLP-1 RAs) were not associated with an increased risk of heart failure hospitalization [22].

GLP-1 RAs:

Based on their half-lives, GLP-1 RAs can be classified as either rapid-acting or sustained-release compounds [23].

Fasting glucose levels are the primary aim of long-acting medications, which also successfully promote weight loss. Short-acting agonists primarily decrease postprandial glucose but have minimal effect on weight [24].

Both liraglutide and semaglutide are categorised as long-acting insulins due to their prolonged effects after administration. In two researches of the broader Liraglutide effect and action in diabetes trial, cardiovascular events in high-risk diabetics were considerably reduced [25].

Important differences between the various GLP-1 RAs are highlighted by these results. Vasoprotection as a cardioprotective mechanism is supported by the SUSTAIN-6 study, which showed a reduction in cardiovascular mortality independent of improvements in heart failure compared to the LEADER trial [26].

In response to promising results shown with GLP-1 and GLP-1 RAs in preclinical research, many smaller randomised trials have investigated the effectiveness of GLP-1 RAs in the treatment of heart failure in people with or without diabetes [27].

Liraglutide caused an average increase of 7 beats per minute in heart rate and was associated with a higher rate of severe cardiac events (10% vs. 3%) than placebo. Similarly, in persons with NYHA II/III heart failure and no diabetes, albiglutide did not increase LVEF, 6-minute walk distance, myocardial glucose absorption, or myocardial oxygen consumption (LVEF 40%). The promising preclinical benefits of GLP-1 in the context of overt heart failure are called into question by these findings [28].

SGLT2 Inhibitors:

A 35 percent relative risk reduction in hospitalisation for heart failure was seen with empagliflozin early on, as seen by a separation of the curves. Indications of an influence on hedonics can be seen in empagliflozin's early impacts on cardiovascular mortality and hospitalisation rates for heart failure. Ketones, produced when SGLT2 is inhibited, may supply energy for the diabetic heart in the presence of insulin resistance [29, 30].

A drop in BMI, BP, sodium intake, oxidative stress, vascular stiffness, and sympathetic nerve activation are all proposed explanations. The Food and Drug Administration (FDA) has approved the first class of glucose-lowering medications (SGLT2i) for the treatment of HFrEF. Major adverse cardiovascular events, including hospitalisation for HF and cardiovascular death, were reduced in patients with type 2 diabetes who used SGLT2i such canagliflozin, dapagliflozin, empagliflozin, and sotagliflozin [31].

CONCLUSION

There is a lack of understanding of the molecular underpinnings and pathophysiology of heart failure in diabetic people. The incidence, prevalence, and outlook for heart failure in diabetic individuals have been proven by certain clinical and epidemiologic data. In the last several decades, diabetic heart disease has risen to prominence as a major cause of death and disability among diabetics.

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