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Diabetes and Heart Failure

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ABSTRACT

Heart failure (HF) in patients with diabetes mellitus has long been considered a consequence of coronary artery disease (CAD). However, recent epidemiological evidence on patients with diabetes showed a significantly increased prevalence of HF in patients with no significant stenosis in the coronary artery. As such, these are thought to be separate entities of diabetic complications. Therefore, HF in patients with diabetes is now considered an independent disease entity of the 'diabetic heart.' The mechanism of 'diabetic heart' could be due to CAD and diabetic cardiomyopathy caused by altered energy metabolism in the myocardium and advanced glycation end-product accumulation, altered calcium handling, and oxidative stress in the myocardium. Recent cardiovascular outcome trials of anti-diabetic medications have shown the protective effects of certain drugs against HF in patients with and without diabetes. In this review, the relationship between diabetes and the treatment and prevention of HF is summarized.

Keywords: Cardiomyopathies; Diabetes complications; Diabetes mellitus; Diabetic cardiomyopathies; Heart failure

INTRODUCTION

Heart failure (HF) is a consequence of coronary artery disease (CAD) in patients with diabetes mellitus (DM). However, since it was discovered that even patients without CAD also have an increased risk of HF, extensive research on "diabetic heart" has been conducted. In South Korea, HF is considered a possible yet overlooked complication of DM based on the recently released Diabetes Fact Sheet—Complications. According to the said document, the prevalence of HF in patients with DM has been constantly increasing, while the incidence of ischemic heart disease or ischemic stroke has been decreasing.[1)]

The American Heart Association (AHA) divides HF into 2 types based on the ejection fraction (EF): HF with reduced EF and HF with preserved EF.[2)] Meanwhile, heart associations worldwide have different classification systems for the HF stages. For example, the AHA classifies HF into 4 stages (A–D) according to structural cardiac abnormalities. In contrast, the New York Heart Association Functional Classification divides HF into 4 functional classes (I to IV) depending on the cardiocirculatory functional status associated with activities of daily living.

In 1972, Rubler et al.[3] first described HF in patients with DM in a case report of 4 diabetic patients with glomerulonephritis who had radiological evidence of myocardial hypertrophy and postmortem findings of myocardial hypertrophy and diffuse fibrosis. In general, diabetic cardiomyopathy is defined as the "structural and functional abnormalities of the myocardium in diabetic patients without CAD or hypertension".[4] However, the mechanism of cardiomyopathy in patients with DM is poorly understood, and there is controversy whether diabetic cardiomyopathy is an actual disease entity or merely a hypothesized disease.

The pathogenesis of HF in patients with DM cannot be explained by a single mechanism. However, the most conspicuous physiological changes in affected patients are the impaired myocardial glucose metabolism and the switching of the heart's primary energy source (fuel) from glucose to less efficient free fatty acids.[5] This altered fuel source leads to impaired systolic ejection performance and left ventricular (LV) and atrial failure. Recent cardiovascular outcome trials (CVOTs) on anti-diabetic medications confirmed the excellent therapeutic effect of sodium-glucose cotransporter-2 (SGLT2) inhibitors in preventing HF and the role of thiazolidinedione (TZD) in significantly increasing the risk of HF.[6]

This article investigates the pathological mechanism of HF in patients with DM, provides an overview of the HF exacerbation and prevention effects of different anti-diabetic drugs, and explores methods for preventing HF in patients with DM.

EPIDEMIOLOGICAL RELATIONSHIP BETWEEN DM AND HF

According to the 2019 Diabetes Fact Sheet by the Korean Diabetes Association, the prevalence of HF has been increasing, while that of vascular diseases, such as myocardial infarction and stroke, has been decreasing. This suggests that HF is a major complication of DM in South Korea.[1] The UK Prospective Diabetes Study reported a correlation between elevated blood sugar and the risk of HF based on the finding that a 1% increase in glycated hemoglobin resulted in a 16% increase in the risk of HF.[7] Similarly, the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease analyzed the risk of HF in 31,546 participants according to the baseline glucose status and found that it increased linearly as the blood sugar level increased from normal to diabetic levels.[8] In an analysis based on the National Health Insurance database, the author followed 9,720,200 Koreans with no HF diagnosis in the 2009 national medical exam for 6 years (2009–2015) and found that subjects with underlying prediabetes and diabetes had a higher risk of HF (8% and 86%, respectively) than those with normal blood sugar levels.[9] These previous studies' findings confirm the positive correlation between blood sugar levels and the risk of HF.

Furthermore, many studies have reported an increased risk of HF in patients with DM. A 1.3-fold risk of HF and a 1.75-fold risk of HF-related hospitalization were shown in patients with DM than those without DM in a sub-analysis of the Studies of Left Ventricular Dysfunction trials, which investigated the HF-preventing effect of enalapril in 4,223 patients with underlying DM by analyzing their risk probability of HF.[10] In an analysis of the database by the Kaiser Permanente North Western Division, a U.S. health plan, the risk of HF was found to increase with age, with a higher prevalence among those with DM compared with those without DM.[11] In clinical trials on blood sugar control and anti-diabetic medication, the prevalence of HF in patients with DM has been reported to range from 10% to 12%.[12]

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The prognosis of HF patients with DM has also been reported. In the I-Preserve study, which examined the effects of irbesartan on HF in 4128 patients with HF for 4.1 years, the risks of cardiovascular mortality and hospitalization for HF (HHF) in patients with DM were 1.59- and 1.75-fold higher, respectively, compared with those in patients without DM.[13] In addition, in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program, designed to investigate the effect of candesartan on HF, patients with DM had a high risk of HHF, and even diabetic patients with preserved EFs had an increased HHF similar to that in non-diabetic patients with reduced EF.[14] Moreover, a sub-analysis of the CHARM program revealed that cardiovascular mortality and the risk of HHF increased by 1.25 times with every 1% increase in glycated hemoglobin.[15]

Conversely, some researchers have argued that HF may be a risk factor for DM. HF-related clinical trials have reported a DM prevalence ranging from 21% to 47%, significantly higher than populations without HF.[12] Matsue et al.[16] also reported that about one-third of the patients hospitalized with HF without a history of DM were found to have prediabetes or diabetes in the tests. In addition, the CHARM program and Eplerenone in Mild Patients Hospitalization and Survival Study in HF (EMPHASIS-HF) trial demonstrated a significant increase in the incidence of DM per 1000 persons among patients with HF and no history of DM compared with the similar age group in the general population (28 vs. 21).[17][18]

In summary, the prevalence of HF among diabetic patients is higher compared to non-diabetic individuals, and the risk of HF increases even after adjusting for several factors, leading to the assumption that HF is a complication of DM. Conversely, patients with HF have an increased risk of DM, possibly signifying that HF is a risk factor for DM. From these findings, it follows that the relationship between DM and HF is bidirectional.[19]

PATHOGENIC RELATIONSHIP BETWEEN DM AND HF

The direct effect of diabetes on cardiomyopathy can be divided mainly into the effect induced by hyperglycemia and insulin resistance. Hyperglycemia causes the accumulation of advanced glycation end product (AGE) in cardiomyocytes, resulting in elevated levels of proinflammatory cytokines that trigger extracellular matrix remodeling and fibrosis.[5] In addition, hyperglycemia and insulin resistance increase oxidative stress and induce myocardial apoptosis. On the other hand, insulin resistance induces lipolysis, leading to myocardial apoptosis and the accumulation of free fatty acids in the myocardium. Furthermore, DM shifts the energy metabolism to utilize free fatty acids instead of glucose, which has the highest myocardial fuel efficiency, degrading the energy efficiency and causing fibrosis in the myocardium. Moreover, insulin resistance leads to abnormal calcium homeostasis in the myocardium, leading to myocardial hypertrophy and abnormal diastolic relaxation.

DM-induced myocardial structural changes were demonstrated in the Strong Heart Study, which analyzed 1,810 diabetic patients and 944 normal controls. Diabetic patients showed greater LV mass and wall thickening and smaller LV systolic chamber size. As such, the LV was smaller and was associated with increased arterial stiffness and decreased myocardial function.[20] Based on the cardiac magnetic resonance spectroscopy of the 46 diabetic patients without hypertension, the LV mass to LV end-diastolic volume ratio was higher than normal controls. They also had increased myocardial fat accumulation and inferior myocardial energy efficiency.[21] In addition, in an analysis of the intraoperative biopsy results of the 46 patients

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with non-diabetic aortic stenosis and the 16 patients with diabetic aortic stenosis, the diabetic patients had a higher rate of myocardial fibrosis and perivascular AGE accumulation.[22]

In conclusion, DM can lead to vasculopathy-induced ischemic cardiomyopathy due to hyperglycemia and insulin resistance. Meanwhile, diabetic cardiomyopathy occurs even without vasculopathy due to lipid toxicity and AGE accumulation, myocardial fibrosis caused by abnormal calcium handling, and myocardial changes due to impaired energy efficiency by shifting the fuel source from glucose to fatty acids (**Figure 1**).[23][24]

TREATMENT OF HF IN PATIENTS WITH DM

The prevalence of HF associated with anti-diabetic medication in clinical trials has a wide range. Specifically, according to the clinical trials on some of the new anti-diabetic agents, dipeptidyl peptidase-4 (DPP-4) inhibitors did not increase the overall prevalence of HF. Saxagliptin is not recommended because of the increased HF risk in the group administered with this in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53).[25] Meanwhile, glucagon-like peptide-1 receptor agonists (GLP-1RA) slightly reduced the risk of HF. Similarly, SGLT2 inhibitors were reported to reduce the risk of HF in studies such as the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME), CANagliflozin cardioVascular Assessment Study (CANVAS), and Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58).[6]

It is also essential to determine to what extent blood sugar levels should be lowered in diabetic patients with HF. In a retrospective study involving 1,447 diabetic patients with HF, the lowest mortality rate was observed in the HbA1c range of 7–8%. Similarly, a study that followed 5,815 patients using the U.S. Veterans Affairs Hospital Database reported that the mortality rate was

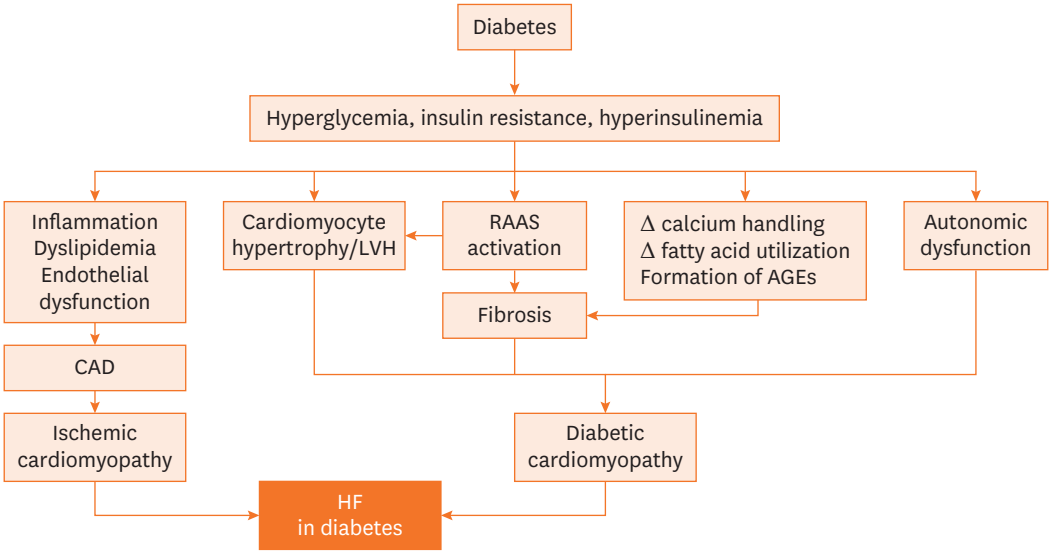

Figure 1. Mechanism of HF in diabetes. Adapted from the article of Dunlay et al. (Circulation 2019;140:e294-324).[24]
AGE = advanced glycation end product; CAD = coronary artery disease; HF, heart failure; LVH = left ventricular hypertrophy; RAAS = renin-angiotensin aldosterone system.

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lowest in the HbA1c range of 7.1–7.8%.[26][27] In the 2019 guidelines, the AHA recommended that blood sugar control in diabetic patients with HF should be individualized, taking into account the patient's clinical and functional status, self-management ability, social support, side effects and costs of medication, risk of hypoglycemia, and treatment burden.[16]

EFFECT OF ANTI-DIABETIC MEDICATION ON HF

Anti-diabetic drugs are considered to have a class effect despite the different individual effects on HF by drugs within the same class. As demonstrated by previous studies and meta-analyses, TZD is not indicated for the treatment of HF.[28] Metformin was initially contraindicated in patients with HF, but this provision was retracted by the Food and Drug Administration in 2006.[29] A meta-analysis of 9 cohort studies involving 34,000 patients revealed that metformin administration reduced the risk of HF by 20% with a risk ratio of 0.80 (95% confidence interval, 0.74–0.87).[30]

Although no consensus has yet been reached regarding the effect of sulfonylureas on HF, no significant increase in the risk of HF has been observed in the insulin supplement therapy group administered with sulfonylureas in the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial. The said trial investigated the cardiovascular outcomes of DM2 patients who underwent intensive medical therapy and percutaneous coronary intervention or medical therapy alone.[31] In the recently published Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) trial, which compared the effects of glimepiride, sulfonylurea, and linagliptin (a DPP-4 inhibitor) on HF, no significant increase in HF-induced hospitalization was observed in the glimepiride group.[32] However, the data from the U.S. Veterans Affairs Hospital Database revealed that a 1.3-fold increase in the risk of HF-induced hospitalization was seen in diabetic patients using sulfonylurea than those with metformin.[33] However, since the CAROLINA trial compared sulfonylurea with metformin, it is difficult to determine the particular HF risk factors of sulfonylureas themselves.

The class effect of DPP-4 inhibitors on HF is challenging to determine. In the SAVOR-TIMI 53 trial, the risk of HF increased in the saxagliptin group.[34] However, a meta-analysis on CVOTs of DPP-4 inhibitors reported that DPP-4 inhibitors do not increase the risk of HF.[35]

Three CVOTs have reported that SGLT2 inhibitors decreased the risk of HF, namely the EMPA-REG OUTCOME, DECLARE-TIMI 58, and CANVAS.[36] Based on the meta-analysis of these CVOTs, SGLT2 inhibitors were found to reduce the risk of HF in patients with and without a history of HF by 31%, leading to the assumption that the effect of SGLT2 inhibitors on HF is very strong. Furthermore, the effect of SGLT2 inhibitors on HF was found to be stronger in patients with more impaired kidney function, suggesting that SGLT2 inhibitors contribute to breaking the vicious cycle of the so-called “cardio-renal spectrum,” where the heart and the kidney mutually affect each other in patients with DM.[37]

The significant effect of SGLT2 inhibitors on HF in patients with DM raised the question if they have the same effect in HF patients without DM. In 2 recently published CVOTs, the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction and the Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure, HF patients

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with and without DM were equally administered with SGLT2 inhibitors, and both studies reported a significantly reduced risk of HF in both groups.[38)39)] In addition, a meta-analysis investigating these 2 studies found that SGLT2 inhibitors reduced the risk of HF by 25%, and the difference between patients with and without DM was insignificant, demonstrating the potential of SGLT2 inhibitors in changing the future therapeutic options for HF patients.[40)]

GLP-1RA improves HF through its positive effect on the myocardium via its anti-inflammatory effect, increased glucose utilization, improved LV function, and decreased ischemic damage.[41)] However, the GLP-1RA CVOTs conducted thus far have reported varying effects on HF. In a meta-analysis investigating 7 different GLP-1RA CVOTs, the odds ratio was calculated at 0.91 (95% CI 0.83-0.99), leading to a 9% reduction in the risk of HF.[42)]

In summary, SGLT1 inhibitors were reported to have the most consistent positive effect on HF, and TZD was contraindicated in patients with HF, while other drugs had varying effects.

HF-RELATED RECOMMENDATIONS IN GUIDELINES ON DM

In recent years, the diabetes management guidelines of the American Diabetes Association have recommended that SGLT2 inhibitors should be prescribed for diabetic patients with HF after metformin. Based on the 2020 guidelines, SGLT2 inhibitors are recommended more specifically for diabetic patients with reduced EF (≤45%),[43)] while TZD should be avoided in patients with HF.

Similarly, the 2019 guidelines of the European Diabetes Association recommend that SGLT2 inhibitors should be utilized as Class I in diabetic patients with HF.[44)] Metformin (class IIa) and GLP-1RA and DPP-4i (class IIb; neutral) are also recommended for the treatment of HF patients, while saxagliptin and TZAs are contraindicated (class III).

Likewise, the treatment guidelines of the Korean Diabetes Association recommend that SGLT2 inhibitors should be prescribed for diabetic patients with HF, while TZD should be avoided.[45)] The AHA emphasizes the need for a multidisciplinary team approach in treating HF and DM. They also highlighted the importance of the roles of social workers, pharmacists, dietitians, exercise therapists, renal specialists, and hospitalization specialists, in addition to primary care physicians.[24)] This suggests medication should be coupled with exercise, diet therapy, and social support when treating HF in patients with DM.

CONCLUSION

HF was a commonly overlooked complication of DM, though it has been extensively investigated in recent years. An increase in the risk of HF in patients with DM has long been known among Korean researchers. In treating diabetic patients with HF, it is important to select agents that are effective in treating HF specifically in diabetic patients and those commonly used to treat HF in the cardiology division. Of these, SGLT2 inhibitors are recommended as the most effective medications. Recent diabetes management guidelines also recommend SGLT2 inhibitors for the treatment of patients with HF.

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In addition to cases of HF with apparent symptoms and reduced EF, which are referred to the cardiology division, asymptomatic cardiomyopathy is completely unpredictable until the occurrence of mortality or morbidity in patients with DM. In addition, when treating patients with DM, it is vital to remember that the risk of HF is already increased even in prediabetes.

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