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Results of SGLT2 inhibitor treatment in patients with Type 2 Diabetes mellitus and heart failure with reduced ejection fraction

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) incidence is increasing all over the world due to obesity. Heart failure (HF) occurs when the functional impairment develops in the myocardium. T2DM may concur with HF and cause its development. The excellent pleiotropic effects of SGLT2 inhibitors within the cardiovascular system make these drugs attractive for the treatment of diabetes in patients with HF.

Materials and Methods: Our study population included 21 patients with New York Heart Association (NYHA) classification II to IV with an ejection fraction less than or equal to 40% and type 2 diabetes mellitus. They were enrolled between February 2019 and February 2020. We collected information on age, sex, eGFR, Left ventricular ejection fraction (LVEF) and duration of empagliflozin usage. Addition of once daily 10 mg of empagliflozin to their treatment applied.

Results: 21 patients with NYHA classification II to IV with an ejection fraction less than or equal to 40% and type 2 diabetes mellitus were enrolled, 19 were male (90.5%). The mean age of the patients was 60 ± 7.21 (Male: 59.11 ± 7.15; Female: 57.50 ± 10.60). The mean use of empagliflozin was 6.90 ± 4.38 months. The mean LVEF in Ecocardiography was 30.52 ± 9.36%. The difference between pro BNP (p=0.205), total cholesterol (p=0.723), triglyceride (p=0.082), HDL (p=0.778), LDL (p=0.808), Hba1c (p=0.643) levels before and after empagliflozin treatment were not statistically significant (p>0.05).

Discussion: Patients with type 2 diabetes and heart failure have been reported to have reduced levels of proBNP and Hba1c with SGLT2 inhibition. In addition, it reduces body weight, blood pressure, CV risk, HF hospitalization. However, in our study, such benefits were not observed in both laboratory and clinical parameters. Large number of patients are needed to research.

Introduction

Type 2 diabetes mellitus (T2DM) incidence is increasing all over the world due to obesity [1]. One of the pathophysiological mechanisms of T2DM is increased glucose reabsorption by kidneys. Heart failure (HF) occurs when the functional impairment develops in the myocardium due to obesity, smoking, coronary heart disease, hypertension [2]. T2DM may concur with HF and cause its development [3]. Some reports suggest that diabetes is found in 40% of HF patients with reduced and up to 45% with preserved ejection fraction [4,5].

The sodium-glucose cotransporter 2 (SGLT2) inhibitors induce glycosuria of nearly 60-90 g/day by blocking SGLT2 mediated proximal tubular glucose reabsorption [6]. SGLT2 inhibitors provide 0.4-0.6% reduction in glycated hemoglobin (HbA1c) levels in diabetic patients. In addition, they lead to reductions in arterial blood pressure (about 3-6 mmHg) and body weight (about 1-2 kg/m^2) [7,8].

The SGLT2 inhibitor, Empagliflozin, improves cardiovascular outcome including death from cardiovascular diseases, nonfatal stroke in patients with T2DM at high risk for cardiovascular events or nonfatal myocardial infarction [9]. Dapagliflozin demonstrated that it provides reduction in the risk of worsening heart failure or death from cardiovascular causes in patients with heart failure independent of the presence of diabetes [10].

EMPA-REG and DAPA-HF trials revealed a reduction in the incidence of acute coronary syndromes [11,12]. The excellent pleiotropic effects of SGLT2 inhibitors within the cardiovascular system make these drugs attractive for the treatment of diabetes in patients with HF [13].

We wanted to investigate the effects of empagliflozin in patients who had diabetes mellitus with heart failure.

Materials and methods

Our study population included 21 type 2 diabetic patients with New York Heart Association (NYHA) classification II to IV with an ejection fraction less than or equal to 40%. All participants involved after signing informed consent. They were enrolled between February 2019 and February 2020. We collected information on age, sex, eGFR, Left ventricular ejection fraction (LVEF) and duration of empagliflozin usage (Table 1). Addition of once daily 10 mg of empagliflozin to their

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treatment applied. In addition, we examined NT-proBNP (N-terminal pro-B-type natriuretic peptide), total cholesterol, triglyceride, HDL, LDL, Hba1c levels and NYHA functional classification, furosemide dosages before and after empagliflozin treatment.

The patients were optimally treated with pharmacological therapy for HF and reduced ejection fraction (HFrEF). Their treatment included angiotensin-converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) and a beta-blocker, as well as diuretics unless contraindicated or not tolerated.

While the categorical variables were described with frequencies and percentages, descriptive statistics were calculated for continuous variables. The Shapiro–Wilk normality test was used to examine whether the continuous variables were distributed normally. Since the data were not normally distributed, Wilcoxon signed rank test was used to compare the median values of two dependent groups. The Pearson chi-square test were used for the analysis of categorical variables. A value of P<.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 25.0 statistical software.

Results

Table 1 demonstrates the baseline characteristics of the patients. 21 type 2 diabetic patients with NYHA classification II to IV with an ejection fraction less than or equal to 40% were enrolled, 19 were male (90.5%). The mean age of the patients was 60 ± 7.21 (Male: 59.11 ± 7.15; Female: 57.50 ± 10.60). While the eGFR levels of 4 patients (19.0%) were between 45-60 mL/min/1.73 m^2, the levels of other patients were above 60 mL/min/1.73 m^2. Before and after empagliflozin treatment, the median of eGFR levels were 77.86 (49.64-126.98) and 73.61 (45.23-110.38), respectively. The mean use of empagliflozin was 6.90 ± 4.38 months. The mean LVEF in Ecocardiography was 30.52 ± 9.36%. 13 of 21 (%61.9) patients were using insulin. The mean duration of diabetes for patients was 7.47 ± 5.77 years, and the mean duration of heart failure for patients was 50.80 ± 44.27 months.

Table 1. Baseline characteristics of patients

	N=21
Sex	
- women	2
- men	19 (90.5 %)
Age (years)	60 ± 7.21
- women	57.50 ± 10.60
- men	59.11 ± 7.15
Duration of Diabetes, years	7.47 ± 5.77
Duration of Heart Failure, months	50.80 ± 44.27
HbA1c, %	7.10 (5.20-10.90)
eGFR<60,mL/min/1.73 m^2 (45-60)	4
Left ventricular ejection fraction, %	30.52 ± 9.36
Duration of empagliflozin usage (months)	6.90 ± 4.38
Furasemid dosage (mg/day)	40.00 (0.00-120.00)

The demonstration of patients' parameters before and after empagliflozin treatment are shown in Table 2. The difference between pro BNP (p=0.205), total cholesterol (p=0.723), triglyceride (p=0.082), HDL (p=0.778), LDL (p=0.808), Hba1c (p=0.643), eGFR (p=0.498) levels before and after empagliflozin treatment were not statistically significant (p>0.05).

During follow-up, none of the patients had urinary tract infections. All patients had had glucosuria except one patient.

Discussion

Empagliflozin has a potential and competitive inhibition of SGLT2 with the highest selectivity compared with the other SGLT2 inhibitors [14]. Recently, it has been revealed that empagliflozin may reduce infarct size in the isolated mouse hearts [15]. The role of AMPK activation is controversial to explain cardioprotective features of empagliflozin [15,16].

EMPA-REG outcome revealed that patients with T2DM at high risk for cardiovascular events who received empagliflozin had a lower rate of the primary composite cardiovascular outcome [9]. Connelly et al. [17] demonstrated that load–independent effects of empagliflozin contribute to improved cardiac function in experimental heart failure with reduced ejection fraction.

The benefits of SGLT2 inhibitors were independent of plasma glucose lowering. SGLT2 inhibitors improved the myocardial oxygen supply because of this pathophysiological mechanism an increase in hematocrit and hemoglobin could be found [18]. This result is remarkable because anemia and/or a reduction in hematocrit is a well-delineated adverse prognostic factor in heart failure. Furthermore, they have been proposed to have a diuretic effect [19,20]. Accordingly, the diuresis induced by SGLT2 inhibition ameliorates the development of LV hypertrophy, provides improved cardiac function independent of loading conditions [17]. In DAPA HF study, independent of glycemic status dapagliflozin improved outcomes in patients with HFrEF. In addition, this study revealed very modest reductions in markers of neurohumoral activation, such as NT-proBNP [10]. There was 48% reduction in NT-proBNP levels after empagliflozin treatment, but probably because of small number of patients there was no statistically significant difference (p=0.205).

In addition, SGLT2 inhibitors play a role in HF, diabetic cardiomyopathy, and the rise in keton body formation and consumption [21]. Empagliflozin increases postprandial glucagon concentration and results in a decrease in insulin levels [22]. Consequently, decrease in insulin-to-glucagon ratio in the vena porta stimulates hepatic ketogenesis. Nonetheless, empagliflozin causes a 2-to 3-fold increase in fasting and postprandial levels of β-hydroxybutyrate [23]. As a result, increased fuel usage of ketone bodies by the heart is related with lower oxygen consumption to provide the same amount of work [21].

Table 2. The demonstration of patients' parameters before and after empagliflozin treatment

N=21	Before empagliflozin treatment	After empagliflozin treatment	p
NT-pro BNP,median,ng/L	1161.00 (49.27-13927.00)	614.00 (73.53-5963.00	0.205
Total colesterol, mg/dL	134.00 (91.00-241.00)	145.00 (74.00-240.00)	0.723
Triglyceride ,g/dL	108.00 (51.00-334.00)	158.00 (57.00-507.00)	0.082
HDL, mg/dL	38.00 (26.00-45.00)	37.00 (25.00-50.00)	0.778
LDL, mg/dL	79.00 (33.00-165.00)	75.00 (19.00-154.00)	0.808
Hba1c, %	7.10 (5.20-10.90)	7.20 (5.10-9.60)	0.643
NYHA functional classification	II	II	0.102
Furosemide dosage, mg	40.00 (0.00-120.00)	40.00 (0.00-120.00)	0.887

Although a relationship between glycosuria induced by SGLT-2 inhibitors and an increased risk for urinary, particularly genital infections has been demonstrated [24], in our study no patient had urinary or genital infection after treatment.

Several limitations must be considered in our study. We had small number of participants which might potentially conclude in a lack of statistical power to find associations.

Conclusion

In conclusion, patients with type 2 diabetes and heart failure have been reported to have reduced levels of proBNP and Hba1c with SGLT2 inhibition. Empagliflozin increases postprandial glucagon concentration and results in a decrease in insulin levels, however we did not demonstrate it, this is a limitation of our study. In addition, it reduces body weight, blood pressure, CV risk, HF hospitalization.

However, in our study, such benefits were not observed in both laboratory and clinical parameters. This situation was thought to be due to the low number of patients. Large number of patients are needed to research.

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