ORIGINAL ARTICLE

Sodium glucose co-transporter-2 inhibitor, Empagliflozin, is associated with significant reduction in weight, body mass index, fasting glucose, and A1c levels in Type 2 diabetic patients with established coronary heart disease: the SUPER GATE study

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Abstract

Background Empagliflozin, a sodium-glucose co-transporter-2 (SGLT-2) inhibitor, yielded significant beneficiaries in the treatment of type 2 diabetes mellitus (T2DM). It is particularly benefited the diabetic subjects with heart conditions.

Aims We aimed to obtain a real-world data about the effects of empagliflozin add-on treatment on metabolic parameters, cardiovascular risk factors, and anthropometric measures in patients with T2DM.

Methods Type 2 diabetic patients with established coronary heart disease whom empagliflozin added to their treatment were enrolled in the study. Anthropometric measures, clinical and laboratory data, were obtained before and at the 6th month of the empagliflozin treatment. All data before and at the 6th month were compared.

Results Body weight ($p < 0.001$), body mass index ($p < 0.001$), waist ($p < 0.001$) and hip ($p < 0.001$) circumferences, systolic blood pressure ($p = 0.006$), heart rate ($p = 0.01$), LDL cholesterol ($p = 0.01$), fasting plasma glucose ($p < 0.001$), and HbA1c ($p < 0.001$) levels were significantly reduced on 6th month of empagliflozin treatment compared to the baseline values. Estimated GFR ($p = 0.66$), serum creatinine ($p = 0.8$), uric acid ($p = 0.40$), total cholesterol ($p = 0.053$), triglyceride ($p = 0.057$), and HDL ($p = 0.09$) levels were not significantly changed.

Conclusions We suggest that empagliflozin treatment may improve anthropometric measures, metabolic parameters, and blood pressure and does not cause deterioration in kidney functions in type 2 diabetic patients with established coronary heart disease.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common challenges of the physicians in daily clinical practice. Due to the chronic and insidious nature of the disease, it may lead to a number of complications, even unnoticed sometimes. It would be too late to reverse these complications when detected lately. Obstacles in accessing medical care may contribute to the development of diabetic complications, especially in COVID-19 pandemic era that we encounter nowadays. Therefore, effective and potentially less harmful treatment strategies should be preferred in the management of the disease.

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors yield significant contribution to the treatment of the patients with T2DM. A recent meta-analysis concluded that this group of anti-diabetic drugs significantly reduced glycated hemoglobin (HbA1c) levels in the diabetic population [1]. Besides its potent activity in decreasing HbA1c and contribution to the better metabolic control in T2DM, SGLT-2 inhibitors also decrease pulmonary artery pressure in diabetic subjects suffer from heart failure [2]. It has been proposed as a novel agent that prevents diabetic cardiomyopathy [3]. Especially, it has beneficial effects on cardiovascular health [4–8]. Not only cardiovascular health but also

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renal health is improved with empagliflozin. Authors found that endothelial dysfunction is improved with empagliflozin treatment in diabetic patients with chronic kidney disease [9].

Since SGLT-2 inhibitors, specifically empagliflozin, provided significant cardiovascular beneficial effects and better diabetic regulation, we aimed to observe its effects on the T2DM patients whom treated with empagliflozin in our university clinic. Therefore, we compared anthropometric measures (i.e., weight, body mass index), physical examination findings (such as systolic and diastolic blood pressures), and laboratory parameters of the patients with T2DM at the beginning of the empagliflozin treatment and at those values at 6th month.

Methods

Design, setting, and population

After getting approval from the ethics committee (approval number 2021/109), patients with T2DM and coronary heart disease who previously applied to Bolu Abant Izzet Baysal University Department of Internal Medicine were enrolled to the SUPER GATE study, and their data were retrospectively analyzed which obtained from institutional database and patients' files. The subjects whose treatments were controlled, and empagliflozin was added to their treatment for blood sugar regulation, and who had used it for at least 6 months were included in the study. The sample size was determined by power analysis. Initially, 108 subjects were eligible and all enrolled but, of those 24, were excluded after application of exclusion criteria, and 12 were excluded since they did not show up in the 6th month control visit. The remaining 72 subjects were enrolled to the study. Considering the missing data, 72 patients were included in the study with a 95% confidence interval (CI) and 20% variability. Those who used the drug irregularly, who stopped using it, who used it for less than 6 months, and those who discontinued the drug due to side effects were excluded from the study.

Anthropometric and laboratory analyses

Age, gender, anthropometric measurements (height, weight, waist circumference, hip circumference, body mass index (BMI)), systolic blood pressure, diastolic blood pressure, heart rate of 72 T2DM patients, glucose, serum creatinine, glycated hemoglobin (HbA1c), estimated glomerular filtration rate (eGFR), aspartate transaminase (AST), alanine transaminase (ALT), c-reactive protein (CRP), serum sodium, potassium, calcium, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein

(HDL) cholesterol, and triglyceride values were recorded retrospectively. All these parameters were recorded as values before empagliflozin treatment and at the 6th month of treatment. BMI was calculated by division of the weight in kg to squared height in meters. The effects of this treatment on all these variables were compared.

Statistical analyses

Statistical analyses were held with SPSS software (SPSS for Windows 20.0, IBM o, Chicago, IL, USA). The average age of the patients was shown as the mean ± standard deviation. The gender ratio was expressed in numbers and percentages. Study variables before and at the sixth month of empagliflozin treatment were compared with paired samples T-test. The p values lower than 0.05 were considered statistically significant.

Results

The study population consisted of 72 subjects: 56 (77.8%) men and 16 (22.2%) women. The average age of the study population was 58.7 ± 8.5 years. The mean duration of T2DM was 9.5 ± 7.8 years in the study population.

The mean weight of subjects at the first examination and at the 6th month control was 83 ± 13 kg and 79 ± 12 kg, respectively. The subjects had an average weight loss of 4 kg at the 6th month compared to the first visit which was statistically significant ($p < 0.001$). The mean body mass index (BMI) of the subjects at the first visit and the 6th month were 30.1 ± 3.8 kg/m^2 and 28.8 ± 3.6 kg/m^2, respectively. BMI of the subjects was decreased by an average of 1.29 kg/m^2, which was statistically significant ($p < 0.001$). The mean waist circumference of subjects at the first examination and the 6th month control was 107.3 ± 8.9 cm and 103.2 ± 3.6 cm, respectively ($p < 0.001$). The mean hip circumference of subjects was reduced from 107.5 ± 8.8 cm at the first examination to 103 ± 9 cm at the 6th month control visit. The decrease in hip circumference was statistically significant ($p < 0.001$).

The mean systolic blood pressures of subjects at the first examination and at the 6th month control visit were 141 ± 23 mmHg and 134 ± 20 mmHg, respectively. Systolic blood pressure decreased by an average of 7 mmHg which was statistically significant ($p = 0.006$). Mean heart rates of subjects at the first examination and at the 6th month control were 74 ± 11 beats/min and 70 ± 13 beats/min, respectively. Heart rate decreased by an average of 4 beats per minute which was statistically significant ($p = 0.01$).

There was no statistically significant change in serum sodium ($p = 0.39$), potassium ($p = 0.62$), calcium ($p = 0.08$), CRP ($p = 0.93$), AST ($p = 0.07$), ALT ($p = 0.06$), total

Table 1 Clinical and the laboratory data of the study population

Parameter	Before empagliflozin treatment	Sixth month of empagliflozin treatment	P
	Mean ± SD		
Weight (kg)	83 ± 13	79 ± 12	**< 0.001**
BMI (kg/m^2)	30.1 ± 3.80	28.6 ± 3.6	**< 0.001**
Waist circumference (cm)	107.3 ± 8,9	103.2 ± 3.6	**< 0.001**
Hip circumference (cm)	107.5 ± 8.8	103 ± 9	**< 0.001**
Systolic BP (mmHg)	141 ± 23	134 ± 20	**0.006**
Diastolic BP (mmHg)	82 ± 14	79 ± 11	0.17
Heart rate (per/minute)	74 ± 11	70 ± 13	**0.01**
Glucose (mg/dL)	196 ± 73	149 ± 54	**< 0.001**
HbA1c (%)	9 ± 1.7	7.8 ± 1.7	**< 0.001**
Urea (mg/dL)	31 ± 9	34 ± 10	**0.005**
Creatinine (mg/dL)	0.92 ± 0.1	0.93 ± 0.1	0.80
eGFR (md/min)	84.8 ± 13	84.2 ± 15	0.66
LDL cholesterol (mg/dL)	100 ± 35	91 ± 34	**0.01**
Na (mmol/L)	138 ± 4.5	139 ± 2.7	0.39
K (mmol/L)	4.6 ± 0.4	4.6 ± 0.5	0.62
Ca (mg/dL)	9.1 ± 0.4	9.2 ± 0.2	0.08
CRP (mg/L)	8.1 ± 3.8	7.9 ± 3.9	0.93
Total cholesterol (mg/dL)	177 ± 46	169 ± 44	0.053
HDL cholesterol (mg/dL)	42 ± 12	55 ± 16	0.09
Triglyceride (mg/dL)	181 ± 114	160 ± 118	0.057
AST	24 ± 6	21 ± 4	0.07
ALT	27 ± 8	23 ± 7	0.06

cholesterol ($p = 0.053$), triglyceride ($p = 0.057$), and HDL ($p = 0.09$) values of the subjects. Clinical and laboratory parameters of the study population are shown in Table 1. Mean serum LDL cholesterol level of subjects at the first examination and the 6th month control was 100 ± 35 mg/dL and 91 ± 34 mg/dL, respectively. Subjects had an average decrease of 9 mg/dL in LDL cholesterol, which was statistically significant ($p = 0.01$).

The mean serum urea level of subjects at the first examination and the 6th month control was 31 ± 9 mg/dL and 34 ± 10 mg/dL, respectively. There was an average increase of 3 mg/dL in urea values of the subjects, and this increase was statistically significant ($p = 0.005$). However, mean serum creatinine levels of the subjects at the first examination, and at the 6th month control visit were 0.92 ± 0.1 mg/dL and 0.93 ± 0.1 mg/dL, respectively ($p = 0.8$). Similarly, mean eGFR values of the subjects at the first examination and at the 6th month control visit were 84.8 ± 13 mL/min and 84.2 ± 15 mL/min, respectively. There was no statistically significant change in eGFR values ($p = 0.66$). Mean fasting glucose levels of subjects at the first examination and at the 6th month control visit were 196 ± 73 mg/dL and 149 ± 54 mg/dL, respectively. The subjects' glucose level decreased by an average of 47 mg/dL which was statistically significant ($p < 0.001$). Figure 1 shows the change in the

study parameters between the initiation and the 6th month of the empagliflozin treatment.

The mean HbA1c level of subjects at the first examination and the 6th month control was 9 ± 1.7% and 7.8 ± 1.7%, respectively. The subjects' HbA1c level decreased by an average of 1.2%, and this was also statistically significant ($p < 0.001$). Figure 2 shows the change in the HbA1c between before and the 6th month of the empagliflozin treatment.

Discussion

Tremendous results of the present report, the SUPER GATE study, are evidence of the following: (a) empagliflozin treatment reduced body weight, body mass index, and waist and hip circumferences significantly, which are associated with type 2 diabetes mellitus and cardiovascular disease; (b) systolic blood pressure and heart rate were significantly reduced by 6 months of empagliflozin therapy; (c) empagliflozin treatment caused a significant decrease in fasting plasma glucose, HbA1c, and LDL-cholesterol levels, which are correlated with diabetic complications; and (d) empagliflozin treatment did not cause a significant change in serum
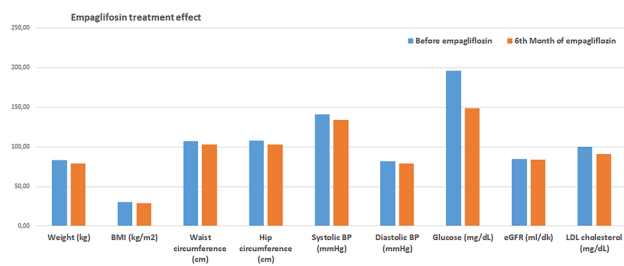
Fig. 1 Change in the study parameters between the initiation and the 6th month of the empagliflozin treatment

creatinine levels and eGFR in type 2 diabetic subjects with coronary heart disease.

Anthropometric measures have been studied in type 2 diabetes mellitus, and it has been established that BMI and waist circumference were associated with the risk of T2DM [10]. These measures also predict the risk of cardiovascular diseases [11]. Therefore, glucose-lowering treatment should be accompanied with measures that reduce body weight, waist circumference, and BMI. The effects of empagliflozin and metformin were compared in subjects with polycystic ovary syndrome, another insulin-resistant state, and authors concluded that empagliflozin caused significant improvements in body weight, waist circumference, hip circumference, and BMI compared to metformin [12]. Treatment duration was 12 weeks, and half of the treatment duration in present study, which was 6 months. Nevertheless, empagliflozin caused 1.4-kg reduction in weight, 1.4-kg/m^2 reduction in BMI, 1.6-cm decrease in waist circumference, and 2 cm of shrinkage in hip circumference [12]. The present study showed that addition of empagliflozin on current
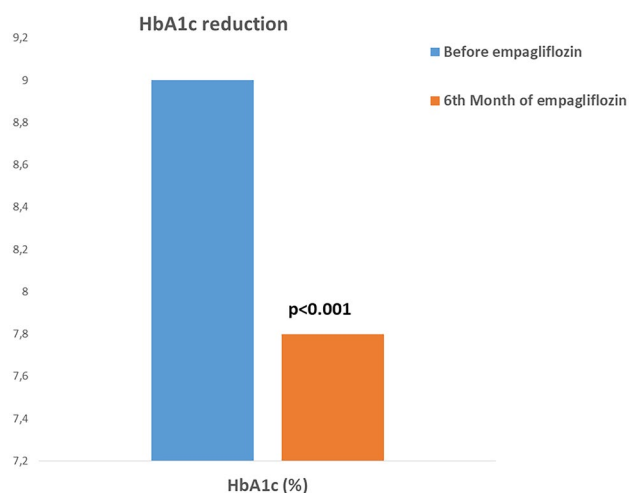

Fig. 2 Change in the HbA1c levels between the initiation and the 6th month of the empagliflozin treatment

T2DM treatment for 6 months provided 3-kg reduction body weight, 1.3-kg/m^2 decrease in BMI, 4.3 cm narrowing in waist circumference, and 2.6 cm shrinkage of hip circumference. Two other studies were suggested similar reductions in body weight, waist circumference, and other anthropometric measures [13, 14]. The results of our report were comparable with the data in literature.

In a study by Shin et al., it has been reported that empagliflozin add-on treatment caused significant reductions in both systolic and diastolic blood pressures [13]. The study of Verma et al. suggested their results by reporting significant improvement in systolic and diastolic blood pressures with empagliflozin treatment [15]. Another study was also reported a significant decrease in both systolic and diastolic blood pressures with SGLT-2 treatment [16]. However, we showed a significant decrease in only systolic blood pressure and heart rate in the present study. The reduction in diastolic blood pressure with empagliflozin was 3.4 mmHg which was not statistically significant.

All SGLT-2 inhibitors, including empagliflozin decreased fasting plasma glucose, HbA1c, and improved serum lipid profile [17]. A recent study reported that 12 weeks of SGLT-2 inhibitor (including empagliflozin) treatment was significantly reduced HbA1c and fasting glucose in the Korean type 2 diabetic population [16]. The authors also found that about 18% of the subjects reached the HbA1c target which was below 7% by 12 weeks of SGLT-2 inhibitor treatment [16]. This rate was 39% in our study. We also confirmed the previous studies by reporting significant reductions in fasting glucose and HbA1c by 6 months of treatment of empagliflozin. Rosenstock et al. reported that empagliflozin reduced HbA1c and fasting glucose significantly when added on to metformin treatment in subjects with type 2 diabetes mellitus [18]. Our results were confirmed the previous studies in literature that showed reductions in metabolic parameters.

These beneficial effects of empagliflozin and other SGLT-2 inhibitor appear to the consequence of improved beta-cell function in diabetic patients [19]. Undesired effects of SGLT-2 inhibitors include urinary tract infection, dehydration, increased urination frequency, and in very rare cases, euglycaemic diabetic ketoacidosis [20]. We did not observe any side effects related to empagliflozin treatment in our study.

In a recent study, authors reported that empagliflozin treatment was associated with deterioration in kidney functions [21]. However, there are also controversial studies in literature. Mortality and morbidity of the diabetic patients with chronic kidney disease were decreased after initiation of empagliflozin treatment [22]. Kadowaki et al. suggested that empagliflozin was improved kidney functions and slowed the rate of decrease in eGFR in the Asian diabetic population received empagliflozin [23]. In present study, the

change in serum creatinine and eGFR was not statistically different after initiation of empagliflozin.

Possible limitations of our work are the single-center nature of the study and the relatively small study population. However, results of the present study, which is a real-world efficacy study, may add significantly to the current literature.

Conclusion

We suggest that empagliflozin treatment may improve anthropometric measures, metabolic parameters, and blood pressure and do not cause deterioration in kidney functions in type 2 diabetic patients with established coronary heart disease.

Declarations

Conflict of interest The authors declare no competing interests.

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