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Evaluation of the Effects of Empagliflozin on Serum Levels of Triglycerides and Cholesterol in Patients with Type 2 Diabetes Mellitus and Hypertriglyceridemia: A Prospective Study

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Abstract

Objective: Sodium-glucose cotransporter -2 (SGLT2) inhibitors may improve lipid panels in addition to lowering blood sugar. This research examined how empagliflozin, an SGLT2 inhibitor, affected triglycerides in type 2 diabetes mellitus (T2DM) patients with hypertriglyceridemia.

Materials and Methods: This prospective study was conducted at the Endocrinology Clinic of Shahid Rahimi Hospital in Khorramabad, Iran, in 2020. Thirty-eight patients were included using convenient sampling. The patients' information including age, gender, body mass index (BMI), Fasting Blood Sugar (FBS), Hemoglobin A1c (HbA1c), 2-hour postprandial blood sugar, serum triglyceride, total cholesterol, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), serum insulin level, serum creatinine Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Blood pressure, and urine albumin before and three months after receiving empagliflozin 10mg tablets were collected from the clinic medical archives and compared using paired t-test in SPSS software version 22.

Results: BMI, microalbuminuria, BUN, FBS, 2-hour postprandial blood sugar, and HbA1c were improved significantly ($P< 0.05$) after treatment with empagliflozin. In terms of lipid panels, triglyceride, cholesterol, and LDL levels were improved significantly after treatment with empagliflozin ($P< 0.05$). HDL levels increased following the treatment but the difference was not statistically significant. There was no linear correlation between HbA1c and HDL ($P= 0.183$) or triglyceride ($P= 0.947$) levels.

Conclusion: Empagliflozin improves triglycerides and cholesterol levels in patients with T2DM in addition to its antihyperglycemic effects. It also reduces BMI, blood pressure, BUN, and microalbuminuria.

Keywords: Type 2 Diabetes mellitus, Dyslipidemia, Sodium-glucose co-transporter 2 inhibitor, empagliflozin

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Introduction

Diabetes mellitus (DM) is a multi-factorial chronic disease that results from various genetic and/or environmental factors (1). In 2017, there were 451 million individuals with DM accounting for approximately 5 million deaths globally. The prevalence is estimated to increase to 693 million by 2045 (2). Type 2 DM (T2DM) comprises around 90 to 95% of DM cases (1). Insulin resistance and insulin secretion insufficiency are the main pathogeneses of T2DM (3). The most significant risk factor for T2DM is excess body fat due to high consumption of fat and sugar and inadequate physical activity (4). Chronic hyperglycemia disturb the microvasculature, resulting in complications such as diabetic nephropathy, retinopathy, and neuropathy (5). Coronary heart disease, cerebrovascular disease, and peripheral artery disease are the major macrovascular complications of T2DM (6). Patients with T2DM have a higher prevalence of dyslipidemia which contributes to their increased risk of cardiovascular disease (4).

Nutrition correction and physical activity are substantial treatment of T2DM. However, most patients may concurrently require pharmacological therapy with at least one of several possible drug classes (7). Inhibitors of Sodium-Glucose Cotransporter 2 (SGLT2) in the proximal tubule of the kidney are a type of glucose-lowering medications with various effects on renal function, plasma volume homeostasis, adiposity, and energy balance (8). There are currently three SGLT2 inhibitors confirmed by the Food and Drug Administration; canagliflozin, dapagliflozin, and empagliflozin. Empagliflozin has the highest specificity and potency compared with others (9).

On the other hand, empagliflozin has several contraindications including serious hypersensitivity reaction, recurrent genito-urinary infections, current or previous gangrene, severe renal impairment, end-stage renal disease, and dialysis which necessities proper administration of this medication (13,14). Lipid metabolism following SGLT2 inhibitor therapy has been evaluated but the findings are controversial.

In some studies, these medications have caused weight loss and reduced liver fat (15,16), while other researchers have reported dyslipidemia associated with SGLT2 inhibitor therapy. This study was conducted to evaluate the effect of empagliflozin on triglyceride levels in patients with T2DM and concurrent hypertriglyceridemia.

Material and methods

This prospective study was conducted in the Endocrinology Clinic of Shahid Rahimi Hospital, Khorramabad in 2020. The study population consisted patients with T2DM who had been referred to the clinic and had the eligibility to receive empagliflozin 10mg tablets according to the guidelines of the American Diabetes Association. Inclusion criteria were Hemoglobin A1c (HbA1c) of greater than 7.5%, age 18 to 70 years, serum triglyceride levels >150 mg/dL, estimated glomerular filtration rate (eGFR)≥ 30 mL/min/1.73 m^2, and informed consent to participate in the study. Patients were excluded if had a positive drug history for receiving triglyceride-lowering medications or had not continued the treatment for at least three months.

Based on the formula below and considering the mean difference of triglyceride= 58.2 (17), α= 0.05, and power= 0.8, the minimum sample size of 8 subjects was calculated. Finally, 38 diabetic patients who met the inclusion criteria were included using census sampling.

After obtaining written and informed consent, the medical files of the patients were read and their demographic data including age, sex, educational level, occupation, age at diagnosis of T2DM, duration of illness, family history of DM, waist circumference, Body Mass Index (BMI), systolic and diastolic blood pressure were recorded in a checklist.

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Laboratory tests including Fasting Blood Sugar (FBS), 2-hour postprandial blood sugar, serum triglyceride and total cholesterol levels, High- Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), HbA1c, serum insulin level, serum creatinine, Blood Urea Nitrogen (BUN), uric acid, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and albumin in the random urine sample, which had been performed for the patients before and three months after receiving empagliflozin tablets (Gloripa®) in a daily dose of 10 mg, were also collected and registered to the checklist.

Statistical analysis

The collected data were analyzed by SPSS software version 22. To compare the variables in different groups, paired t-test was used. The significance level was set at 0.05 for all statistical tests.

Ethical considerations

This study was conducted with the permission of the Research Ethics Committee of Lorestan University of Medical Sciences with the ethical code IR.LUMS.REC. 1399.263. Written, informed, and voluntary consent was obtained from all participants in the study. The checklists were designed anonymously and the patients' personal information remained confidential.

Results

In this study, 38 patients with T2DM and hypertriglyceridemia were included. Twenty patients (52.6%) were male and 18 (47.4%) were women. The mean (±SD) age of the patients was 54.08 (± 8.89). The mean duration of diabetes was 6.29 (±3.51) years. Also, thirty-two patients (84.2%) had a family history of diabetes. Other demographic data are listed in Table 1.

Also, 13 patients (34.2%) had a previous history of retinopathy, 1 patient (2.6%) had a history of diabetic foot, and 1 patient (2.6%) had a history of stroke, while none of the patients had a history of nephropathy. In terms of cardiovascular diseases, 6 patients (15.8%) had a positive history, including 3 patients (50%) with coronary artery disease, 1 (16.17%) with ischemic heart disease, 1 (16.17%) with a previous history of coronary angiography, and the type of cardiovascular involvement was unclear in 1 patient. The history of hyperlipidemia was positive in 34 patients (89.5%).

In terms of the history of consuming hypoglycemic agents, 31 patients (81.6%) used metformin, 1 patient (2.6%) sitagliptin/metformin and pioglitazone, 2 patients (2.5%) gliclazide extended-release, 13 patients (34.2%) gliclazide, and 11 patients (28.9%) glibenclamide and sitagliptin. Only 1 patient (2.6%) had a history of taking insulin. Regarding the history of blood pressure medications, 23 patients (60.5%) had a history of taking blood pressure medications. The type of medication used was losartan potassium in 14 patients (60.9%), metoprolol tartrate in 2 (8.7%), losartan potassium and metoprolol tartrate in 2 (8.7%), losartan and amlodipine in 3 patients (13%), losartan potassium, metoprolol tartrate and nitroglycerin in 2 patients (8.7%).

Table 1. Demographic data of the diabetic patients

Variable		Frequency	Percent
Sex	Female	18	47.4
	Male	20	52.6
Marital status	Married	36	94.7
	Single	0	0
	N/A	2	5.3
Education levels	Illiterate	5	13.2
	Less than 12th grade	6	15.8
	High school diploma	20	52.6
	Associate's degree	3	7.9
	Bachelor's degree	4	10.5

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Thirty-three patients (86.8%) used lipid-lowering medications in the studied population. In all of them, the type of lipid-lowering medication was atorvastatin. There was a statistically significant difference between patients' BMI ($P< 0.001$) before and after treatment with empagliflozin.

There was no statistically significant difference between serum insulin levels before and after treatment ($P= 0.265$). However, there was a statistically significant difference between 2-hour postprandial blood sugar levels ($P= 0.046$), HbA1c levels ($P< 0.0007$), and FBS levels ($P< 0.0009$) before and after treatment (Table 2).

There was no statistically significant difference between the blood AST ($P= 0.735$) and ALT ($P= 0.277$) levels of patients before and after treatment.

There was a statistically significant difference between triglyceride levels before and after treatment ($P< 0.0009$). There was a statistically significant difference between blood cholesterol levels before and after treatment ($P< 0.0008$). The LDL levels decreased significantly after treatment with empagliflozin ($P= 0.001$). However, no statistically significant difference was found between blood HDL levels before and after treatment ($P= 0.524$).

There was no statistically significant difference between urine albumin levels before and after treatment ($P= 0.097$). There was a statistically significant difference between the serum uric acid levels before and after treatment with empagliflozin ($P= 0.004$). There was a statistically significant difference between patients' systolic blood pressure before and after treatment ($P= 0.002$) but we found no statistically significant difference between diastolic blood pressure before and after treatment and empagliflozin ($P= 0.190$).

Table 2. Clinical and laboratory data of the diabetic patients before and after treatment with empagliflozin

Variable		Frequency	Mean	Standard deviation	*P*-value*	Difference in means
BMI (kg/m^2)	Before	38	32.3542	4.98228	<0.001	-1.282
	After	38	31.0729	4.56902		
Urine albumin (mg/L)	Before	38	33.4474	44.29611	0.097	-9.3396
	After	36	23.7778	14.10595		
Serum insulin level (mIU/L)	Before	33	16.7091	15.70562	0.265	-3.6828
	After	38	13.0263	9.18838		
2-hour postprandial blood sugar (mg/dL)	Before	8	272.5000	71.40028	0.046	-52.4
	After	10	220.1000	63.20417		
AST (U/L)	Before	19	26.5263	16.76759	0.735	-3.641
	After	26	22.8846	7.51173		
ALT (U/L)	Before	19	41.7368	23.71086	0.277	-6.5768
	After	25	35.1600	13.50210		
Triglyceride (mg/dL)	Before	36	263.0556	62.26668	<0.001	-52.395
	After	36	210.6667	53.35381		
Cholesterol (mg/dL)	Before	36	190.2778	51.33677	0.001<	-16.44
	After	36	173.8333	46.70852		
LDL (mg/dL)	Before	36	102.000	33.5465	0.001	-12.834
	After	36	89.1667	26.5744		
HDL (mg/dL)	Before	37	34.5081	11.3635	0.524	1.242
	After	37	35.7568	4.05795		
HbA1c (%)	Before	37	8.6676	1.49016	<0.001	-1
	After	37	7.6676	0.70909		
FBS (mg/dL)	Before	37	176.7297	42.27861	0/001<	-27.009
	After	37	149.7027	23.94190		
Serum creatinine (mg/dL)	Before	34	1.3691	1.54625	0.823	0.09
	After	34	1.4526	1.41214		
Uric acid (mg/dL)	Before	35	5.2486	1.46214	0.004	-0.71
	After	35	4.5383	0.89667		
Systolic blood pressure (mmHg)	Before	37	132.2973	9.54482	0.002	-4.59
	After	37	127.7027	8.04455		
Diastolic blood pressure (mmHg)	Before	37	81.4865	7.80535	0.190	-1.89
	After	37	79.5946	7.48873		

***: paired T-test**

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Based on the Pearson correlation coefficient, no significant linear relationship was observed between blood HbA1c and HDL (*P*= 0.49, r= 0.179) and triglyceride levels (*P*= 0.185, r= 0.232) before treatment. Also, no significant linear relationship was observed between blood HbA1c and HDL (*P*= 0.183, r= 0.224) and triglyceride levels (*P*= 0.947, r= 0.011) after the intervention.

Discussion

This study was conducted to evaluate the effect of empagliflozin, an SGLT2 inhibitor, on triglyceride levels in patients with T2DM and concurrent hypertriglyceridemia. The results of this study showed that BMI significantly improved after treatment with empagliflozin. Similarly, Neeland et al. showed beneficial effects of empagliflozin on reducing weight and adiposity indices (18). Kovacs et al. found that empagliflozin as an add-on to pioglitazone or pioglitazone + metformin decreased weight in patients with T2DM (19). The results of this study showed that FBS, 2-hour postprandial blood sugar, and HbA1c significantly improved after treatment with empagliflozin. In agreement with our findings, Inzucchi et al. reported that empagliflozin, as an add-on to metformin, reduced HbA1c and body weight (20). Rosenstock et al. investigated the impact of empagliflozin added to basal insulin in patients with T2DM. After 78 weeks, empagliflozin remarkably reduced HbA1c and weight compared with the placebo (21). SGLT2 inhibitors enhance fat utilization and reduce insulin resistance by polarizing M2 macrophages (22).

In mouse models, it has been observed that insulin levels significantly increase following the administration of empagliflozin (23). We investigated this matter in human subjects but similar to previous clinical studies, no significant difference was found between insulin levels before and after treatment with empagliflozin (24). The results of this study showed that microalbuminuria significantly improved after treatment with empagliflozin. Wanner and colleagues found that in patients with T2DM at high risk for cardiovascular diseases, empagliflozin led to a decrease in the progression of renal involvement, however, in their study, empagliflozin showed no remarkable effect on the rate of incident albuminuria (25). The serum uric acid-lowering effect of SGLT2 inhibitors has been detected in patients with T2DM (26).

This effect, which is probably exerted through the reduction of oxidative stress (27), was also observed in our study. In terms of the lipid panel, triglyceride, cholesterol, and LDL levels significantly improved after treatment. However, there was no significant linear correlation between HbA1c and HDL, and triglyceride. The effects of empagliflozin on lipid panels in diabetic patients have been investigated by several researchers. Lund et al. based on pooled data from phase 3 randomized trials concluded that empagliflozin increased LDL, HDL, and decreased triglycerides in patients with T2DM compared with placebo (28).

In contrast to our findings, Ozcelik and colleagues found no significant difference between lipid profile parameters before and after treatment with empagliflozin (17). The effect of empagliflozin on lipid profile seems controversial. Overall, empagliflozin switches energy metabolism from carbohydrate to lipid usage leading to moderately increased ketone production and LDL levels. However, it decreases intestinal cholesterol absorption, which successively increases LDL- and macrophage-derived cholesterol fecal excretion (29). In this study, there was a statistically significant difference between patients' systolic blood pressure before and after treatment. Similarly, Tikkanen and co-authors reported significant effects of empagliflozin on reduction in blood pressure and HbA1c levels (30).

The physiologic mechanism of blood pressure lowering with SGLT2 inhibitors has been ascribed to several factors. Insulin raises sodium chloride reabsorption in the proximal tubule and SGLT may contribute to this effect.

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Also, improved glycemic control and reduction in arterial stiffness are potential mechanisms (31,32). This study had some limitations; due to the COVID-19 pandemic, diabetic patients had less frequently attended the clinic for follow-up, hence the number of subjects who had visited the clinic for the 3-month follow-up was limited. In addition, there are certainly many known and unknown factors that may affect the lipid profile of patients with T2DM so further studies with larger sample sizes are required to control these factors.

Conclusion

Considering the results of the present study, it can be concluded that empagliflozin, in addition to its antihyperglycemic effects, is a beneficial therapeutic option for improving lipid panels in patients with T2DM. Further studies with larger sample sizes are recommended to investigate the wide-range effects of SGLT2 inhibitors.

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Conflict of Interest

The authors attest that they have no conflict of interest to disclose.

Authors' contributions

SCh: Title ideation, Data gathering, Manuscript writing

MA: Data gathering. Manuscript writing

GM: Statistical analysis, Manuscript writing

AKR: Project managing, Data gathering, Manuscript writing.

All the authors critically revised the manuscript, agree to be fully accountable for the integrity and accuracy of the study, and read and approved the final manuscript.

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