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METABOLIC EFFECT OF DAPAGLIFLOZIN IN REDUCING SERUM LOW DENSITY LIPOPROTEIN CHOLESTEROL AND SERUM TRIGLYCERIDE

General Medicine

Dr. Ranjeet Kumar Singh M D (General Medicine) H.O.D. Dept. of Medicine Central Hospital Ramgarh

Dr. Sushil Kumar* M D (General Medicine) Assistant Professor, Dept. of Medicine, Mednirai Medical College and Hospital Palamu *Corresponding Author

Dr. Abha Kumari MD Community Medicine

ABSTRACT

Objective: The aim of this study is to assess the effects of dapagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, on serum triglyceride and low-density lipoprotein (LDL) cholesterol levels in patients with type 2 diabetes mellitus (DM). **Methods:** A total of 40 patients with type 2 DM, who were followed up regularly in out patient department Central Hospital Ramgarh, were evaluated retrospectively. In these patients, Dapagliflozin was added to their regular treatment for glycaemic control. The patients anthropometric measurements, glycaemic regulation status, and serum LDL cholesterol and triglyceride levels were retrieved from the system records. A statistical analysis of drug effects was performed using the repeated measures analysis of covariance test, keeping the effects of HbA1c and body mass index (BMI) covariates constant. **Results:** In addition to the improvement in fasting blood glucose levels, HbA1c, and body weight of the patients there is reduction by 10.5 mg/dL and 43.04 mg/dL was observed in serum LDL cholesterol and triglyceride levels, respectively. The evaluation of BMI and HbA1c covariates together revealed a statistically significant reduction in triglyceride level (p=0.032 and p=0.008, respectively). **Conclusion:** Besides glycaemic control and weight loss, addition of dapagliflozin to the type 2 DM therapy is associated with an improvement in serum LDL Cholesterol and triglyceride levels, suggesting that together with other benefits, SGLT2 inhibitors appear to provide an additional benefit of reducing the risk of cardiovascular diseases.

KEYWORDS

Cardiovascular diseases, dapagliflozin, hyperlipidaemia, SGLT2 inhibitor

INTRODUCTION

There are six identified SGLT (sodium glucose co-transporter) proteins in humans, of which the SGLT1 and SGLT2 receptors have been studied more thoroughly in recent years. Despite the outstanding sequence similarity between SGLT1 and SGLT2, they show different physiological and biochemical properties. While SGLT1 is primarily expressed in the intestines, SGLT2 is most abundant in the renal cortex, where it plays an essential role in renal glucose reabsorption. SGLT2 inhibitors, including dapagliflozin, canagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, ertugliflozin and empagliflozin, have been studied in several clinical studies for the treatment of type 2 diabetes mellitus. Their selectivity for the SGLT2 receptor shows significant variance. While empagliflozin is 2500×, ertugliflozin is 2000×, dapagliflozin is 1200×, canagliflozin is 250×, sotagliflozin is only 20× more selective for the SGLT2 receptor over SGLT1, which may cause significant differences in the mechanism of action [1].Diabetes mellitus (DM) is associated with an increased risk of cardiovascular diseases (CVD), which is the major cause of morbidity and mortality in patients suffering from type 2 DM. (2,3). Other risk factors for CVD include hypertension, hyperlipidemia, obesity, and smoking. Hyperlipidemia is a common metabolic disorder among patients with type 2 DM (4).Although the risk of CVD is reduced by decreasing LDL cholesterol to target levels, a substantial proportion of patients with type 2 DM fail to achieve target LDL cholesterol levels. Hence, a significant number of patients suffering from type 2 DM remain at risk of CVD (5). With this in view, new therapeutic options for type 2 DM provide us with new opportunities. Sodium glucose cotransporter 2 (SGLT2) inhibitors help to provide glycemic control by inhibiting glucose reabsorption through proximal renal tubules(6) In addition, SGLT-2 inhibitors show favorable effects on blood pressure, body weight, arterial stiffness, visceral adiposity, albuminuria, and plasma uric acid concentration (7). Considering the effects of SGLT-2 inhibitors on lipid parameters, in addition to studies showing an increase in both high-density lipoprotein (HDL) and LDL cholesterol levels, there are studies reporting an increase in HDL cholesterol but not in LDL cholesterol (7, 8). The underlying hypothetic mechanisms of SGLT2 inhibitors beyond their antidiabetic effects are summarized in Figure 1.

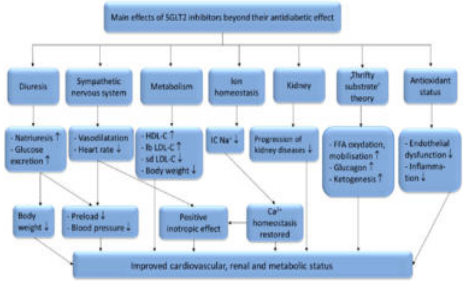

Figure 1. The systematic effects of SGLT2-inhibitors. HDL-C: high-density lipoprotein cholesterol; lb LDL-C: large buoyant low-density lipoprotein cholesterol; sd LDL-C: small dense low-density lipoprotein cholesterol; TG: triglycerides; IC Na+: intracellular sodium-ion; FFA: free fatty acids; ↑: increased amount; ↓: decreased amount.

In the present study, we evaluated the effects of dapagliflozin that was added for 24 weeks to current treatment plans of patients with type 2 DM, who were receiving oral anti diabetics (OAD) and/or insulin on lipid parameters

METHODS

The present study included patients with type 2 DM aged 40–70 years, followed up in the outpatient department at central hospital Ramgarh from March 2019 to October 2019. Dapagliflozin was added to the OAD and/or insulin therapy. We were able to reach a total of 58 patients. Among these patients, those without the third and sixth month follow-ups were excluded from the study. The data of the remaining 40 patients were retrospectively reviewed and statically analyzed.

Inclusion Criteria:

Patients with diabetes mellitus with age between 40-70 years.

Exclusion Criteria:

Young onset diabetes(< 30 years),Type 1 Diabetes, Diabetic nephropathy patients on dialysis and renal transplant.

All patients were followed up by the same specialist using the same follow-up and treatment protocol Weight measurements were performed in the morning on an empty stomach at baseline and follow-up visits. Body mass index (BMI) was computed as a ratio of weight to square of height in metre (kg/ m2).For biochemical analyses, all blood samples were obtained from venous samples between 08:00 and 10:00 am after overnight fasting. Fasting blood glucose (FBG) and lipid profile were assessed using an automated enzymatic method, and HbA1c was assessed using the turbidimetric inhibition immunoassay (Roche Diagnostics, Mannheim, Germany).Insulin administration and

dosage remain unchanged at baseline and follow up visit.

Main Points:

- SGLT-2 inhibitors show favorable effects on blood pressure, body weight, arterial stiffness, visceral adiposity, albuminuria, and plasma uric acid concentration.
- Substantial proportion of patients with type 2 DM fail to achieve target lipid levels.
- Results of studies on the effects of SGLT2 inhibitors on LDL-cholesterol and triglyceride have varied.
- The positive effect of Dapagliflozin on lipid parameters is an important result in reducing the risk of CVD in patients with type 2 diabetes.
- Administration and dosage regimens were unchanged at baseline and follow-up visits.

Statistical Analysis

Continuous variables were expressed as mean standard deviation, whereas categorical variables were expressed as frequency (%). The level of significance was predetermined to be 0.05 within the 95% confidence interval for all tests. The Shapiro–Wilk test was used for the Gaussian distribution. As for the univariate analysis, the chi-squared test and paired t-test were used, while the Wilcox- on signed-rank test was used when the condition for normality was not met. Keeping the effects of covariates HbA1c (difference as percentage) and BMI (numeric difference) constant, the change in LDL cholesterol and triglyceride levels between before and after treatment according to the medication was analyzed by repeated measures analysis of covariance (ANCOVA). After providing normality and homogeneity of variances for ANCOVA (using the Box-M test), the assumption of regression curves of the independent variable (drug) and covariates (HbA1c and BMI) being homogeneous (interactions >0.05) was provided. In addition, the linearity of LDL cholesterol and triglycerides with the covariates (HbA1c and BMI) was reviewed. All analyses were performed using the IBM Statistical Package for the Social Sciences Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The mean age of 40 patients, of whom 17 (42.5%) were female and 23 (57.5%) were male, was 52.85±9.08 years. The mean duration of DM was 8.07±4.12 years. Laboratory results and anthropometric measurements are summarized in Table 1. The mean weight loss was 1.63±0.32 kg. The pre and post treatment changes in FBG, HbA1c, LDL cholesterol, and triglyceride levels were significantly lower in our study group (Table 1). Of the patients, 26 (65%) were not receiving statins or fibrates, and 14 (35%) were receiving either of the drugs (Table 2).

By keeping the HbA1c and BMI covariates constant over the 6-month treatment period from baseline, a decrease was observed in the LDL cholesterol levels during that time. However, this decrement was not caused by the drug (p=0.663 for the drug with HbA1c as covariate and p=0.525 for the drug with BMI as covariate) (Table 3, Figure 1). By keeping the HbA1c and BMI covariates constant over the 6-month treatment period from baseline, a decrease was also observed in triglyceride levels during that time. Drug use as well as time had an effect on this decrement(p=0.032 for the drug with BMI ascovariate)(Table 3 Figure 2)

DISCUSSION

SGLT-2 inhibitors cause a loss of approximately 240–320 calories/day by means of urinary glucose excretion at an average of 60–80 g/day (9). In a study conducted on the patients who were added SGLT-2 inhibitors to their treatment, a weight loss up to 1.1 –1.8 kg on average was observed in the 6-month follow-up period (10). In the present study, the mean weight loss was 1.63 kg, which is consistent with the literature. Among the parameters of glycemic regulation, the expected reduction in FBG and HbA1c values with addition of SGLT-2 inhibitors is 20–30 mg/dL and 0.5%–1%, respectively (11). In the present study, the mean decrease in FBG and HbA1c was 47.14 ng/ dL and 2.1%, respectively. In patients receiving DPP-4 inhibitors together with SGLT-2 inhibitors, the average reduction in HbA1c has been reported between 1.1% and 1.5% (12). In our study group, the substantial proportion of the patients was receiving DPP-4 inhibitors (75%). The response to antidiabetic medications is usually far above the expected levels in patients with high baseline HbA1c and FBG values. Many studies have demonstrated that using statins for either primary or secondary prevention remarkably reduces cardiovascular events and related deaths (13, 14). SGLT-2 inhibitors, which are among the new generation OADs, are OADs with insulin-independent glucose-reducing effect. They lead to calorie loss while reducing glucose absorption through proximal tubules. In case of fasting, calorie deficit is compensated using lipids instead of glucose (15, 16). Various clinical trials performed with SGLT-2 inhibitors have reported increased LDL cholesterol (1.5%–6.3%) and HDL cholesterol (5.5%–9.2%) levels, but decreased triglyceride (1%–9.4%) levels (17). In the present study, we observed that the LDL cholesterol level decreased by 10.5 mg/dL (8.68%), and triglyceride levels decreased by 43.04 mg/dL (19.58%). The evaluation of LDL cholesterol alone revealed that the decrement reached the level of statistical significance; however, considering it together with the changes in BMI and HbA1c, the decrement was not statistically significant. In this sense, the results of the present study are consistent with the literature. The decrement in triglyceride levels was significant both alone and in the presence of other covariates (HbA1c and BMI). The improvement in triglyceride levels might be associated with weight loss and improved insulin sensitivity.(18) The present study has some limitations. First, it is a single-center small-scale study. Second, the study has a retrospective design. Moreover, HDL and total cholesterol measurements were not available as the patients were followed up according to their treatment protocol.

CONCLUSION

Addition of SGLT-2 inhibitors in the treatment of type 2 DM improves the lipid profile in addition to glycemic regulation. In this sense, it will be reasonable to mention an additional effect of SGLT-2 inhibitors in reducing the risk of CVD in patients with type 2 DM. Dapagliflozin, a SGLT-2 inhibitor, included in the treatment plan of patients with type 2 DM and dyslipidemia not only provides glycemic regulation, but it also shows a beneficial effect on lowering of LDL Cholesterol and triglyceride level.

Figure and Tables

Figure 1. a, b. Change in low-density lipoprotein cholesterol levels with time and drug use in the presence of (a) HbA1c covariate and (b) body mass index covariate

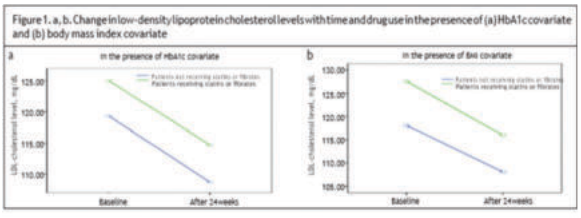

Table 1. Univariate analyses and descriptive values for the parameters

Parameter	Baseline	After 24 weeks	p
Age (year), mean±SD	52.85±9.08		
Duration of DM (year), mean±SD	8.07±4.12		
Gender, n (%)			
Female	17 (42.5)		0.352*
Male	23 (57.5)		
Cigarette smoking, n (%)			
Nonsmoker	27 (67.5)		0.001*
Quitted	8 (20)		
Current smoker	5 (12.5)		
Body weight (kg), mean±SD	88.85±15.04	87.22±14.72	0.012**
BMI (kg/m²), mean±SD	32.26±4.50	31.70±4.44	0.014**
SBP (mmHg), mean±SD	126.50±14.59	125.75±10.09	0.520**
DBP (mmHg), mean±SD	80.12±5.60	79.62±5.11	0.562**
FBG (mg/dL), mean±SD	219.62±70.38	172.48±53.08	0.001***
HbA1c (%), mean±SD	10.07±1.70	7.97±1.24	0.001**
LDL (mg/dL), mean±SD	121.23 ±35.81	110.70±35.95	0.041**
TG (mg/dL), mean±SD	219.72±150.63	176.68±125.84	0.002***
Creatinine (mg/dL), mean±SD	0.72±0.19	0.72±0.20	0.513**
eGFR (mL/min per 1.73 m²), mean±SD	101.64±14.13	101.71±14.60	0.938**

*chi-squared test; **Student' s t-test; ***Wilcoxon signed-rank test. DM: diabetes mellitus; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; LDL: low-density lipoprotein; TG: triglyceride; eGFR: estimated glomerular filtration rate; SD: standard deviation

Figure 2. a, b. Change in triglyceride levels with time and drug use in the presence of (a) HbA1c covariate and (b) body mass index covariate

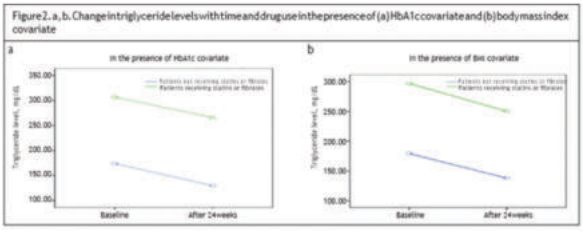

Table 2. Drug groups, which might affect lipid levels, used by patients at the beginning of the study

Drug Groups	(%)
Metformin	87
DPP4 inhibitors	75
SU	40
Insulin	20
TZD	5
GLP-1 A	2.5
Statin	20
Fibrate	15
Thiazide	10
Beta blocker	10
LT4	7.5

SU: sulfonylurea; DPP4: dipeptidyl peptidase 4; TZD: thiazolidinedione; GLP-1A: glucagon-like peptit-1 analog; LT4: levothyroxine.

Table 3. Effects of dapagliflozin on LDL cholesterol and triglyceride levels according to statin and fibrate use in the presence of covariates (BMI and HbA1c)

		Mean±SD	p
Statin and fibrate nonusers	LDL baseline	118.30±37.22	0.145
	LDL final	107.40±36.53	
	TG baseline	180.63±75.00	0.006
	TG final	136.42±45.41	
Statin and fibrate users	LDL baseline	127.10±33.95	0.374
	LDL final	117.30±35.72	
	TG baseline	294.00±223.58	0.214
	TG final	253.20±187.66	

LDL: low-density lipoprotein; TG: triglyceride; SD: standard deviation

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