Original Article

Effect Of Dapagliflozin On Lipid Profile In Type-2 Diabetes Mellitus

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Abstract

Objective: Aim was to determine the effects of Dapagliflozin on lipid profile in patients of Type-2 Diabetes Mellitus.

Study Design: Randomized placebo-controlled trial

Place and Duration:

Methods: This randomized placebo-controlled trial was carried out at Combined Military Hospital, Peshawar from 1st February 2022 to 30th April 2022 on type-2 diabetes patients having dyslipidemia. Baseline blood samples for serum LDL-C, HDL-C and triglycerides were collected after a 12- hour fast. Patients were randomized to receive either Dapagliflozin 10 mg OD or placebo on top of their existing regular antidiabetic and lipid lowering medications. Lipid profile was rechecked after 12 weeks. Changes in Lipid Profile from baseline was the primary outcome. Secondary outcomes were changes in HBA1c, Fasting Blood Sugar, body weight and blood pressure.

Results: Patients mean age was 55.9 ±12.39 years and had mean BMI 29.7 ±10.88 kg/m^2. There were 17 (65.4%) males and 9 (34.6%) were females. 10 (38.5%) patients were educated and 19 (73.1%) cases were from rural areas. 11 (42.3%) patients had smoking history. HTN, IHD and obesity were the most common comorbidities among all cases. LDL-C was significantly lower in the Dapagliflozin group compared to the placebo group from 4.6±3.16 to 1.9±1.7 mmol/l , with a p value of 0.002 for each. We also found reduction in triglycerides in group I from 3.2±1.4 to 2.1±1.11 mmol/l while increased in HDL-C was noted 2.1±1.8 to 3.7 ±2.5 mmol/l. With a p value of 0.005, the levels of HbA1c, fasting plasma glucose (FPG), and systolic blood pressure (SBP) were significantly lower after 12 weeks.

Conclusion: We found that patients with T2DM experienced significant lipid lowering effects from Dapagliflozin as compared to placebo. Significant reduction in LDL-C, Triglycerides, Systolic BP, Fasting Plasma Glucose, HbA1c and increased HDL-C were also noted in Dapagliflozin group.

Keywords: Dapagliflozin, Lipid Profile, Diabetes Mellitus, LDL-C

INTRODUCTION

Diabetes mellitus has emerged as one of the most urgent and prevalent problems in recent years. It is now the seventh leading cause of death in the USA and globally, accounting for 5.2 million deaths worldwide with a mortality rate of 82.4 per 100,000[1]. Additionally, diabetes mellitus (DM) increases the risk of cardiovascular disease (CVD), the leading cause of death for people with DM [2]. Cardiovascular deaths account for 44% of deaths in those with type1DM and 52% of deaths in type2 DM [3]

In view of this, cardiovascular protection has become one of the objectives of therapy in diabetes [4]. A great interest is devoted to the study of extra-glycemic effects of glucose lowering medications. The sodium-glucose co-transporter-2 inhibitor (SGLT2i) dapagliflozin was found to lower blood pressure by about 3-5 mmHg, body weight by about 2-

3 kg, and HbA1c by about 0.6-0.9% in phase III randomized clinical trials [5]. The EMPA-REG Outcome study [6] and Phase III RCTs both linked SGLT-2i treatment to a drop in blood triglycerides, an increase in HDL cholesterol, and a marginal rise in LDL cholesterol. On the other hand, Fadini et al in a recent randomized placebo controlled trial [7] found that dapagliflozin has no effect on blood HDL-C, LDL-C and triglycerides.

So in summary, evidence from the Western countries suggests that dapagliflozin increases levels of LDL-C and HDL-C and reduces triglycerides. However, such data is inconsistent globally and limited from our country and as it is generally established that Asians may respond differently from whites due to genetic variations in drug metabolism at the hepatic enzyme and drug transporter level [8]. This study was therefore carried out to determine the effects of dapagliflozin on LDL-C, HDL-C and triglycerides in a Pakistani cohort.

MATERIALS AND METHODS

This randomized placebo-control trial was conducted at Department of Medicine of Combined Military Hospital, Peshawar, Pakistan from 1st February 2022 to 30th April 2022 and comprised of 26 patients of T2DM. Enrollment of patients started afterapproval from Ethics Review Committee of the Institute.

Inclusion criteria were:
1) 30-75 years old male or female patients
2) diagnosed with Type 2 Diabetes having disease duration of at least 6 months
3) undergoing treatment with oral antidiabetic medications.
4) having dyslipidemia
Importantly patient had to be on a stable statin dose for 3 months at least if already taking statins.

Exclusion criteria were:
patients on insulin therapy, type 1 diabetes, Chronic Kidney Disease patients with eGFR less than 30ml/min/1.73 m^2, Chronic Liver Disease, Heart Failure with NYHA III-IV, active tuberculosis or other infectious diseases, recurrent Urinary Tract Infections, history of hypotension, electrolyte imbalance, pregnancy or lactation.

After obtaining patients' informed consent in writing, demographic information was collected. Then the patient's baseline body weight, height and blood pressure were measured and recorded. Blood samples were collected for estimation of serum LDL-C, HDL-C and triglycerides after a 12-hour fast. Blood samples were also taken for estimation of the patients' baseline HBA1C and fasting plasma glucose. Patients were then assigned to either of the two groups, each comprising of 13 patients using nonprobability convenience sampling technique. The first group was to receive Dapagliflozin 10 mg daily after breakfast whereas the second group was to be given placebo at the same time, on top of their regular medicines required for the underlying diseases. Treatment was continued for a total of 12 weeks, during which period the patients were followed up on 4 weekly intervals. At each visit, compliance to treatment was assessed and possible side effects to treatment were noted. At the end of 12 weeks period, the patients' body weight, height, blood pressures were measured and all the above-mentioned blood tests were repeated.

Data was collected and analyzed on an intention to treat basis using SPSS (Statistical Programme for the Social Sciences) version 23.0 (SPSS Inc., Chicago, IL, USA). The data were measured using the Kolmogorov-Smirnov normal test, described using the mean standard deviation and percentage (%) for variables that followed a normal distribution. The two groups' measurement data were compared using an independent sample -test, and their pre- and post-treatment outcomes were compared using a paired sample -test. We compared the observed data using the chi-square test. Bilateral tests at the 0.05 level of significance were used for all statistical analyses.

Sample size calculation: 13 patients on Dapagliflozin, and 13 on placebo (total 26) required, assuming mean change in LDL of 0.1 ± 6.1 with placebo and 9.1 ± 9.5 with Dapagliflozin, as previously reported by Fadini et al [7]. For this calculation, a 2-tailed test was used with 95% CI and 20% margin of error.

RESULTS

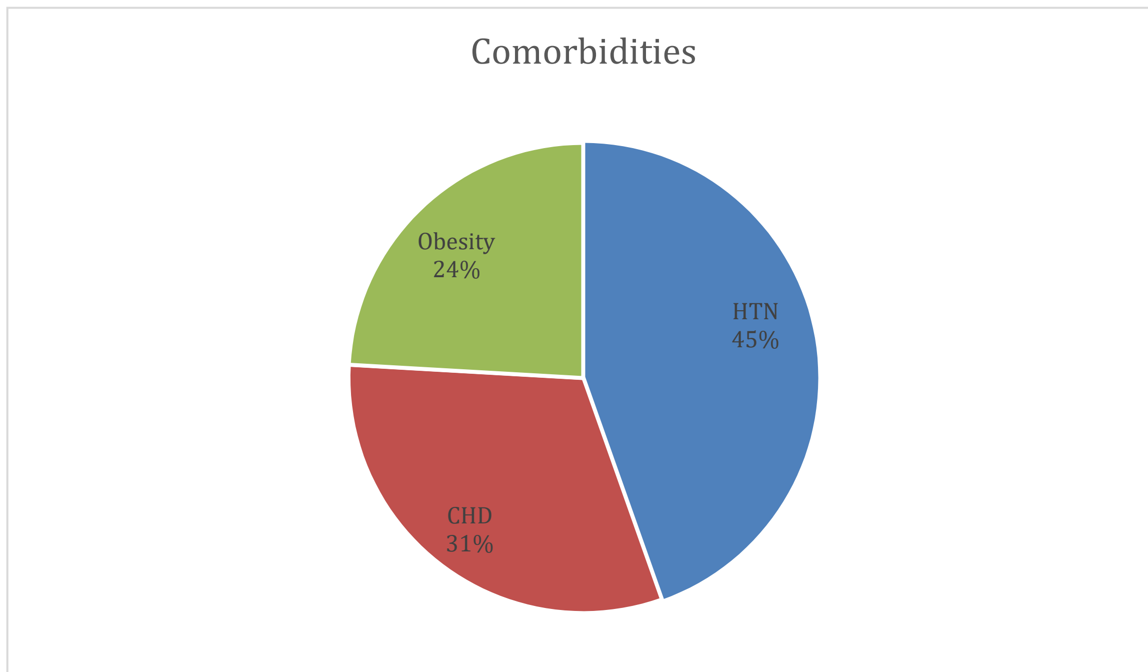
Patients mean age was 55.9 ±12.39 years and had mean BMI 29.7 ±10.88 kg/m^2. There were 17 (65.4%) males and 9 (34.6%) were females. 10 (38.5%) patients were educated and 19 (73.1%) cases were from rural areas. 11 (42.3%) patients had smoking history.

Table-1: The enrolled cases' demographics

Variables	Frequency (n=26)	Percentage
Mean age (years)	55.9 ±12.39	
Mean BMI (kg/m^2)	29.7 ±10.88	
Gender		
Male	17	65.4
Female	9	34.6
Education status		
Educated	10	38.5
Non-educated	16	61.5
Residence		
Rural	19	73.1
Urban	7	26.9
Smoking History		
Yes	11	42.3
No	15	57.7

HTN, CHD and obesity were the most common comorbidities among all cases.

Figure-1: Percentage of comorbidities among all cases



With a p value < 0.002, the levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides was observed considerably decreased in group I as compared to group II, while increase in HDL-C was noted from 2.1±1.8 to 3.7 ±2.5 mmol/l. (Table 2)

Table-2: Comparison of LDL-C, Triglycerides and HDL-C in both groups

Baseline	**Dapagliflozin**	**Placebo**
LDL-C (mmol/l)	4.6±3.16	4.0±1.16
triglycerides (mmol/l)	3.2±1.4	3.8±2.7
HDL-C (mmol/l)	2.1±1.8	1.8±1.9
After Final Follow up		
LDL-C (mmol/l)	1.9±1.7	3.9±4.17
triglycerides (mmol/l)	2.1±1.11	3.1±2.5
HDL-C (mmol/l)	3.7 ±2.5	2.8±1.17

Following 12 weeks, there was a substantial reduction in HbA1c, fasting plasma glucose (FPG), blood pressure levels and weight with a p value <0.005 in Dapagliflozin group as compared to placebo. (Table 3)

Table-3: Effect of Dapagliflozin and placebo on HbA1c, FPG, Systolic and Diastolic Blood Pressure and weight.

Baseline	**Group I**	**Group II**
HbA1c (%)	8.75±6.48	7.7±4.12
Fasting plasma glucose (FPG) (mmol/l)	11.1±6.17	12.4±6.15
Diastolic BP (mmHg)	86.4±14.60	85.8±6.55
Systolic BP (mmHg)	145.17±8.67	144.9±10.94
Weight (kg)	88.2±15.79	86.4±15.42
After Final Follow up		
HbA1c (%)	6.7±3.54	7.3±2.19
Fasting plasma glucose (FPG) (mmol/l)	5.9±4.7	7.2±2.57
Diastolic BP (mmHg)	81.5±7.77	84.6±5.33
Systolic BP (mmHg)	138.5±12.49	142.5±11.23
Weight (kg)	81.6±17.37	84.14±6.37

DISCUSSION

Inhibitors of SGLT-2 have been shown to increase LDL-C levels in several phase III studies [9]. Larger sample sizes were used in these research. Treatment with SGLT-2 inhibitors has been associated with an increase in LDL-C, which could increase patients' atherogenic risk. Contrarily, the majority of studies have demonstrated that SGLT-2 inhibitors reduce triglycerides and increase HDL-C levels, hence reducing atherogenic risk [10]. Lipid-lowering drugs such fibrates and omega-3 fatty acids have a tendency to elevate LDL-C, possibly due to decreased lipid transfers between TG-rich lipoprotein (TRL)-TG with LDL-C [11,12]. In light of this, it should come as no surprise that the decreased production of cholesterol-poor LDL particles was also linked to the decreased levels of triglycerides seen in those who used SGLT-2 inhibitors. In addition to lowering insulin resistance via decreasing body weight and glucose toxicity, SGLT-2 inhibitors may enhance LDL-C concentrations through other mechanisms. Having a higher insulin sensitivity encourages the conversion of very low-density lipoprotein-C to low-density lipoprotein-C [13].

In current study 26 patients of type-2 diabetes were presented. Patients mean age was 55.9 ±12.39 years and had mean BMI 29.7 ±10.88 kg/m^2. There were 17 (65.4%) males and 9 (34.6%) were females. 10 (38.5%) patients were educated and 19 (73.1%) cases were from rural areas. These results were in line with the previous studies. [14,15] The study's key end-point, Lipid profile was found to be significantly altered by dapagliflozin compared to placebo.

With a significance level (p) of 0.005, our study found a substantial reduction in HbA1c and fast plasma glucose (FPG). Also systolic blood pressure (SBP), diastolic blood pressure (DBP), and low-density lipoprotein cholesterol (LDL-C) levels dramatically decreased while HDL-C levels rose. Dapagliflozin has a significant effect on lipid metabolism, according to new studies. Dapagliflozin is also known to boost HDL cholesterol while decreasing triglyceride and uric acid levels in the blood [16,17]. Patients treated with SGLT-2i have been shown in one study [32] to experience a large increase in LDL-C levels, while simultaneously seeing a drop in small and dense LDL levels, which is helpful for atherosclerotic illnesses [18].

It is believed that cholesterol efflux from macrophages has a pro-atherosclerotic effect because it is a component of the reversal of cholesterol transport, which prevents cholesterol buildup in the arterial wall [19,20]. The levels of HDL cholesterol, the size of HDL particles, the activity of PON1 and ARE, two enzymes that control HDL's antioxidant properties, or CETP, the enzyme in charge of cholesterol metabolism, were all unaffected. Although research has connected inflammatory processes, lipid content, and HDL particle size to lipid profile in many populations, the precise cause of lipid profile is still unknown [21]. The observed decrease in lipid profile cannot be readily accounted for because dapagliflozin only minimally decreased IL-6 and had no impact on lipid profile or HDL subfractions.

In order to increase the amount of glucose discharged in urine, the innovative oral hypoglycemic drug dapagliflozin prevents the kidney's proximal tubules from reabsorbing glucose. SGLT2is have been shown to boost weight loss, enhance blood pressure, lipid profiles, and hyperuricemia without raising the risk of hypoglycemia, and lower HbA1c levels. [22] The global health catastrophe they have sparked is mostly due to both type 2 diabetes and obesity [23]. A key component of controlling type 2 diabetes is maintaining a healthy weight [24]. Liraglutide and dapagliflozin, two potent hypoglycemic drugs, are often prescribed by doctors in China to help type 2 diabetics control their weight. In an animal model of heart failure with preserved ejection fraction, treatment with liraglutide decreased cardiometabolic dysregulation and improved cardiac performance, whereas treatment with dapagliflozin improved glucose management but had only a little effect. [25].

CONCLUSION

We found that patients with T2DM experienced significant lipid lowering effects from Dapagliflozin as compared to placebo. Significant reduction in LDL-C, Triglycerides, Systolic BP, Fasting Plasma Glucose, HbA1c and increased HDL-C were also noted in Dapagliflozin group.

REFERENCE

1. Global Burden of Disease Study 2015. Global burden of disease study 2015 (GBD 2015) results. Seattle: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http:// ghdx.healthdata.org/gbd-results-tool. Accessed 9 Aug 2018.

2. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation. 2018;137(12):e67–e492.

3. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. WHO multinational study group. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. Diabetologia. 2001;44(Suppl 2):S14–21.

4. Lathief S, Inzucchi SE. Approach to diabetes management in patients with CVD. Trends Cardiovasc Med. 2016;26(2):165–79.

5. Plosker GL. Dapagliflozin: a review of its use in patients with type 2 diabetes. Drugs. 2014;74(18):2191–209.

6. Zaman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.

7. Fadini GP, Bonora BM, Zatti G, et al. Effects of the SGLT2 inhibitor dapagliflozin on HDL cholesterol, particle size, and cholesterol efflux capacity in patients with type 2 diabetes: a randomized placebo-controlled trial. Cardiovasc Diabetol. 2017;16(1):42. Published 2017 Apr 4. doi:10.1186/s12933-017-0529-3

8. Kim, K., Johnson, J.A. and Derendorf, H. (2004), Differences in Drug Pharmacokinetics Between East Asians and Caucasians and the Role of Genetic Polymorphisms. The Journal of Clinical Pharmacology, 44: 1083-1105. https://doi.org/10.1177/0091270004268128

9. Hach T, Gerich J, Salsali A, Kim G, Hantel S, Woerle H, Broedl UC. Empagliflozin improves glycemic parameters and cardiovascular risk factors in patients with type 2 diabetes (T2DM): pooled data from four pivotal phase III trials. Diabetologie und Stoffwechsel. 2014;9:p142.

10. Nauck MA. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. Drug Des Devel Ther. 2014;8:1335–80.

11. Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. J Lipid Res. 2002;43:1363–79.

12. von Schacky C. A review of omega-3 ethyl esters for cardiovascular prevention and treatment of increased blood triglyceride levels. Vasc Health Risk Manag. 2006;2:251–62.

13. Annuzzi G, De Natale C, Iovine C, Patti L, Di Marino L, Coppola S, Del Prato S, Riccardi G, Rivellese AA. Insulin resistance is independently associated with postprandial alterations of triglyceride-rich lipoproteins in type 2 diabetes mellitus. Arterioscler Thromb Vasc Biol. 2004;24:2397–402.

14. Calapkulu M, Cander S, Gul OO, Ersoy C. Lipid profile in type 2 diabetic patients with new dapagliflozin treatment; actual clinical experience data of six months retrospective lipid profile from single center. Diabetes Metab Syndr. 2019 Mar-Apr;13(2):1031-1034

15. von Eckardstein A, Nofer JR, Assmann G. High density lipoproteins and arteriosclerosis. Role of cholesterol efflux and reverse cholesterol transport. Arterioscler Thromb Vasc Biol. 2001;21(1):13–27.

16. Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, French BC, Phillips JA, Mucksavage ML, Wilensky RL, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med. 2011;364(2):127–35.

17. Ronsein GE, Vaisar T. Inflammation, remodeling, and other factors affecting HDL cholesterol efflux. Curr Opin Lipidol. 2017;28(1):52–9.

18. Y. Saisho, “SGLT2 inhibitors: the star in the treatment of type 2 diabetes?” Diseases, vol. 8, no. 2, p. 14, 2020.

19. C. M. Apovian, J. Okemah, and P. M. O'Neil, “Body weight considerations in the management of type 2 diabetes,” Advances in Therapy, vol. 36, no. 1, pp. 44–58, 2019.

20. S. M. Fruh, “Obesity: risk factors, complications, and strategies for sustainable long-term weight management,” Journal of the American Association of Nurse Practitioners, vol. 29, no. S1, pp. S3–S14, 2017.

21. C. Withaar, L. M. G. Meems, G. Markousis-Mavrogenis et al., “The effects of liraglutide and dapagliflozin on cardiac function and structure in a multi-hit mouse model of heart failure with preserved ejection fraction,” Cardiovascular Research, vol. 117, no. 9, pp. 2108–2124, 2021.

22. T. Hayashi, T. Fukui, N. Nakanishi et al., “Dapagliflozin decreases small dense low-density lipoprotein-cholesterol and increases high-density lipoprotein 2-cholesterol in patients with type 2 diabetes: comparison with sitagliptin,” Cardiovascular Diabetology, vol. 16, no. 1, p. 8, 2017.

23. Z. Hao, X. Huang, H. Shao, and F. Tian, “Effects of dapagliflozin on serum uric acid levels in hospitalized type 2 diabetic patients with inadequate glycemic control: a randomized controlled trial,” Therapeutics and Clinical Risk Management, vol. Volume 14, pp. 2407–2413, 2018.

24. A. Jiang, Z. Feng, L. Yuan, Y. Zhang, Q. Li, and Y. She, "Effect of sodium-glucose co-transporter-2 inhibitors on the levels of serum asprosin in patients with newly diagnosed type 2 diabetes mellitus," Diabetology and Metabolic Syndrome, vol. 13, no. 1, p. 34, 2021.

25. S. A. Cha, Y. M. Park, J. S. Yun et al., "A comparison of effects of DPP-4 inhibitor and SGLT2 inhibitor on lipid profile in patients with type 2 diabetes," Lipids in Health and Disease, vol. 16, no. 1, p. 58, 2017.