EVALUATING IMPACT OF EMPAGLIFLOZIN ON LIPID PROFILE OF PATIENTS OF TYPE 2 DIABETES MELLITUS

Nauman Wazir[1], Shafqat Ur Rehman[2]

ABSTRACT

OBJECTIVES

To assess the effect of two doses, i.e., 10 mg and 25 mg of empagliflozin, on the lipid profile of patients with type 2 diabetes mellitus (T2DM) with suboptimal glycemic control on maximal doses of metformin and sitagliptin.

METHODOLOGY

The study design was a randomized, open-label clinical trial. Fifty-nine adult patients of T2DM who were already on 2000 mg of Metformin and 100 mg of Sitagliptin and were having suboptimal glycaemic control (HBA1C > 7% <12%) were randomly allocated in 1:1 ratio to two groups, one group receiving 10 mg (Group A) and the other group receiving 25 mg of Empagliflozin (Group B) as an additional treatment. Fasting lipid profiles, including total cholesterol (TC), low-density cholesterol (LDL-C), high-density cholesterol (HDL-C) and triglycerides (TG), were taken before and 12 weeks after the addition of empagliflozin in both the groups.

RESULTS

Total patients in group A were 31, and their mean age was 51.48±4.29 years. In group B, there were 28 patients, whose mean age was 52.39 ± 5.20 years. There was an increase in TC, LDL-C and HDL-C and a reduction of TG in both the groups after treatment with empagliflozin, but it was not statistically significant (p > 0.05).

CONCLUSION

Both doses of Empagliflozin (10 and 25 mg) modestly elevates total cholesterol, LDL-C and HDL-C and modestly reduce triglyceride levels in T2DM patients, but the change is not statistically significant.

KEYWORDS: *Empagliflozin, Type 2 diabetes mellitus, Total cholesterol, Low -density cholesterol, High-density cholesterol, Triglycerides*

How to cite this article:
Wazir N, Rehman SU. Evaluating Impact of Empagliflozin on Lipid Profile of Patients of Type 2 Diabetes Mellitus. J Gandhara Med Dent Sci. 2022;9(3): 20-24
https://doi.org/10.37762/jgmds.9-3.174

Correspondence

[1]Nauman Wazir, Assistant Professor,Department of Medicine, MTI Lady Reading Hospital Peshawar
+92-336-9190857
nauman.wazir@yahoo.com
[2]Assistant Professor, Department of Medicine, Naseer Teaching Hospital, Peshawar

INTRODUCTION

Empagliflozin is a member of a new group of anti-diabetic medications called the sodium-glucose co-transporter2 inhibitors (SGLT2-I). SGLT2-I are pharmacologic inhibitors of SGLT2 function. SGLT2-I counteract hyperglycemia in patients with T2DM by reducing renal glucose reabsorption and therefore increasing urinary glucose excretion.[1] Dyslipidemia is a common co-morbidity of patients with T2DM that increases cardiovascular morbidity and mortality.[2] A large-scale landmark clinical study, EMPA-REG OUTCOME, which evaluated the safety of empagliflozin, has shown it to significantly reduce the risks for primary cardiovascular

endpoints, including cardiovascular mortality.[3] The EMPA-REG OUTCOME trial and the CANVAS program showed that treatment with Empagliflozin or Canagliflozin increased both low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C).[4] The possible mechanism of action is thought to be the involvement of the inhibition of glucose reabsorption caused by SGLT2 inhibitors, leading to a compensatory enhancement of lipid metabolism, thereby influencing the changes in lipid profiles as secondary effects. It is also reported previously that SGLT2 inhibitors reduce glucose metabolism while increasing the use of other energy sources such as ketones, lipids and branched-chain amino acids.[5] One study showed that treatment SGLT2-I cause a small increase in LDL-C and HDL-C levels, while triglyceride (TG) and small dense LDL levels tend to decrease modestly.[6] However, few detailed investigations on such changes in lipid profiles caused by SGLT2 inhibitors have been performed.[7,8] Managing diabetes mellitus requires a holistic view. As well as the effect on glucose levels, it is necessary to look at the effect of individual anti-diabetic medication on diabetes-related co-morbidities such as dyslipidaemia. To our knowledge, no local study has been done to particularly see the effects of empagliflozin on lipid profiles of T2DM patients. Therefore, in this study, we aimed to view the impact of empagliflozin on the lipid profile of Pakistani T2DM patients.

METHODOLOGY

In this study conducted between January 2020 and December 2020 at the Department of Medicine, Naseer Teaching Hospital, Peshawar, consecutive patients who were previously diagnosed to have T2DM and had sub-optimal glycaemic control (HbA1C of > 7% and < 12%) with metformin 2000 mg daily and sitagliptin 100 mg daily were included. Other inclusion criteria were age more than 18 years and both genders. Exclusion criteria were patients with impaired renal function (estimated Glomerular Filtration rate of < 45ml/), pregnancy, chronic liver disease, cerebrovascular event or acute coronary syndrome. A total of 84 patients met the inclusion criteria, of which 7 were excluded as per the exclusion criteria, and the rest (seventy-six) were included in the study. These were randomly allocated in a 1:1 ratio into two groups. Group A received Empagliflozin 10 mg on top of the previous treatment, and group B received Empagliflozin 25 mg in addition to the previous treatment. Both the groups were followed up for 12 weeks during the study duration of 1 year. Seven patients of group A and 10 patients of group B were lost to follow up. Therefore, at the end of the study duration, the follow-up data of 59 patients (31 in group A and 28 in group B). Fasting lipid profiles, including total cholesterol (TC), low-density cholesterol (LDL-C), High-density cholesterol (HDL-C) and triglycerides (TG), were obtained before and 12 weeks after intervention with empagliflozin treatment. The SPSS 23.0 version was used to analyse the data. Mean ± SD were calculated for quantitative variables like age, TC, LDL-C, HDL.C and TG. Percentages and frequency were calculated for qualitative variables like gender. Analysis was done by doing paired sample t-test to determine group mean differences between descriptive variables of the two intervention groups at 12 weeks and baseline. To see the difference in outcome between the two intervention groups, an independent sample t-test was used. A value for p-value < 0.05 was considered statistically significant.

RESULTS

A total of 59 patients (29 males and 30 females) were included in the study. In Group A, there were 31 patients, out of which 13 patients were male, and 18 were female, and the mean age was 51.48 ± 4.29 years. In Group B, there were 28 patients, out of which 16 patients were male, and 12 were female, and the mean age was 52.39 ± 5.20 years. The clinical and demographic variables of Group A and Group B are depicted in Tables 1 and 2, respectively. The between-group difference is shown in table 3.

Table 1:Clinical and Demographic Data in Patients Receiving Empagliflozin Treatment in Group A.

Parameter		Baseline	Group A	P-value
Age (years)		51.48±4.29		
Gender	Male	13(41.9%)		
	Female	18(51.9%)		
Duration of diabetes, (years)		6.5±2.3		
TC, mg/dl		222.5±14.0	224.8±13.7	0.20
LDL-C, mg/dl		132.5± 14.0	134.6±13.4	0.24
HDL-C mg/dl		39.1±2.9	39.8±3.6	0.17
TG mg/dl		252.5±14.0	250.5±17.5	0.32

Abbreviations: TC=Total cholesterol, LDL-C=Low-density cholesterol, HDL=C=High-density cholesterol, TG=Triglycerides, SD=Standard deviation

Table 2: Clinical and Demographic Data in Patients Receiving Empagliflozin Treatment in Group B.

Parameter		Baseline	Group B	P-Value
Age		52.39± 5.20		
Gender	Male	16(57.1%)		
	Female	12(42.9%)		
Duration of diabetes, years		6.8±2.5		
TC, mg/dl (SD)		215.3±12.0	218.3±11.2	0.14
LDL-C, mg/dl (SD)		130.2±12.0	133.2±12.1	0.29
HDL-C mg/dl (SD)		41.0±2.4	42.1±3.6	0.12
TG mg/dl (SD)		212.3±12.0	208.8±10.2	0.17

Abbreviations: TC=Total cholesterol, LDL-C=Low-density cholesterol, HDL=C=High-density cholesterol, TG=Triglycerides, SD=Standard deviation

Table 3:Comparison of Pre and Post Added Empagliflozin Therapy Differences in Parameters between Group A and Group B.

Parameter	Change from Baseline Treatment		P-Value
	Group A	Group B	
Δ TC mg/dl (SD)	2.2 ± 9.4	2.9 ± 10.4	0.77
Δ LDL-C mg/dl (SD)	2.0 ± 9.3	3.8 ± 16.2	0.60
Δ HDL-C mg/dl (SD)	0.72 ± 2.9	1.1 ± 3.6	0.66
Δ TG mg/dl (SD)	2.0 ± 11.3	3.5 ± 13.6	0.63

Abbreviations: Δ TC= Change in total cholesterol, Δ LDL-C= Change in low-density cholesterol, Δ HDL=C= Change in high-density cholesterol, Δ TG= Change in triglycerides, SD=Standard deviation.

DISCUSSION

Our study showed that although both the doses of empagliflozin, i.e, 10 mg and 25 mg, increased the TC, LDL-C and HDL-C from baseline, this increase was not statistically significant. Our study also revealed that empagliflozin in both doses also reduces TG levels, but this reduction was not statistically significant. Similar observations have been seen in a Turkish study.[9] Several studies that have observed empagliflozin's potential role on lipid metabolism have ended up with a negative effect .[10,11] The study of Briand et al.[12] showed that empagliflozin increased LDL cholesterol levels moderately and increased ketone production by switching energy metabolism from carbohydrate to lipid utilisation. Similarly, a meta-analysis of empagliflozin trials demonstrated increased LDL-C in the group treated with empagliflozin .[13] In contrast to the previously mentioned evidence, our study showed no significant change in lipid profiles between the baseline and post-treatment with empagliflozin. A possible explanation could be a positive effect in terms of HbA1C decrease causing improvement in lipid metabolism that neutralised the negative effect on the lipid profile by empagliflozin, given the fact that the HbA1C decrease in our study is much more (Mean HbA1C 10.11±0.79 % baseline vs 8.67±1.03 % after empagliflozin 10 mg treatment, and 9.39±0.56 % baseline vs 8.32±0.76 % after empagliflozin 25 mg treatment) than that reported earlier in the literature.[14,15] A meta-analysis of 34 randomised control trials showed that the treatment with SGLT2-I (Dapagliflozin, Canagliflozin, Empagliflozin) increased HDL-C (mean change 1.93 mg/dL), LDL-C (mean change 3.5 mg/dL) and decreased serum triglycerides (mean change 7.8 mg/dL).[16] This meta-analysis showed that although the mean differences in the increase in LDL-C and HDL-C and the mean difference in the decrease of TG were statistically significant for canagliflozin, in line with our study, the mean increase in LDL-C was not statistically significant for empagliflozin for which only mean an increase in HDL-C and mean reduction in TG were significant. Our study agrees with another meta - analysis which showed that although there was an increase in LDL-C and HDL-C after treatment with empagliflozin, the mean difference was not statistically significant.[17] The in-between differences of increase in TC, LDL-C and HDL-C and decrease of TG in the two groups treated with 10 mg and 25 mg of empagliflozin were minimal and not statistically significant. Given the considerable positive effect on cardiovascular outcomes, it is prudent to assume that the SGLT2-I cause a qualitative rather than merely a small quantitative effect on the lipid sub-components.[18] This has been recently shown to suppress atherogenic small dense LDL-C and increase the blood levels of large buoyant LDL-C, which are less atherogenic. They have also been shown to increase HDL2-C, a favourable cardiometabolic marker. A recent meta - analysis showed that they modestly improve all components of diabetic dyslipidaemia (small dense LDL particles, triglycerides, HDL- C) and, therefore, possibly reduce cardiovascular risk.[16] They are indeed recommended as a first - line treatment after metformin by American Diabetes Association for T2DM patients with atherosclerotic cardiovascular disease and congestive cardiac failure.[19]

LIMITATIONS

A relatively small sample size and short follow - up duration are potential limitations of this study.

CONCLUSION

Empagliflozin modestly elevates total cholesterol, LDL-C and HDL-C and modestly reduces triglyceride levels in T2DM patients, but the change is not statistically significant.

CONFLICT OF INTEREST: None

FUNDING SOURCES: None

REFERENCES

1. Gallo LA, Wright EM, Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. Diabetes & vascular disease research. 2015 Mar;12(2): 78 – 89.
2. Vergès B. Pathophysiology of diabetic dyslipidaemia: where are we? Diabetologia. 2015 May;58(5): 886 – 99 .
3. Zinman B, Wanner C, Lachi JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. New England Journal of Medicine. 2015 Nov 26;373(22):2117–28.
4. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017 Aug 17;377(7):644–57.
5. Santos-Gallego CG, Requena - Ibanez JA, San Antonio R, Ishikawa K, Watanabe S, Picatoste B, et al. Empagliflozin Ameliorates Adverse Left Ventricular Remodeling in Nondiabetic Heart Failure by Enhancing Myocardial Energetics. Journal of the American College of Cardiology. 2019 Apr;73(15):1931–44.
6. Filippas-Ntekouan S, Tsimihodimos V, Filippatos T, Dimitriou T, Elisaf M. SGLT-2 inhibitors: pharmacokinetics characteristics and effects on lipids. Expert Opinion on Drug Metabolism & Toxicology. 2018 Oct 25;1–9.
7. Inagaki N, Goda M, Yokota S, Maruyama N, Iijima H. Effects of Baseline Blood Pressure and Low-Density Lipoprotein Cholesterol on Safety and Efficacy of Canagliflozin in Japanese Patients with Type 2 Diabetes Mellitus. Advances in therapy. 2015 Nov;32(11):1085–103.
8. Halimi S, Vergès B. Adverse effects and safety of SGLT-2 inhibitors. Diabetes & Metabolism. 2014 Dec;40(6):S28–34.
9. Ozcelik S, Celik M, Vural A, Aydin B. The effect of low and high dose empagliflozin on HbA1c and lipid profile in type 2 diabetes mellitus: A real-world data. Northern clinics of Istanbul. 2019 Dec 2;7(2):167–73.
10. Kohler S, Salsali A, Hantel S, Kaspers S, Woerle HJ, Kim G, et al. Safety and Tolerability of Empagliflozin in Patients with Type 2 Diabetes. Clinical Therapeutics. 2016 Jun;38(6):1299–313.
11. Lund SS, Sattar N, Salsali A, Crowe S, Broedl UC, Ginsberg HN. Potential relevance of changes in haematocrit to changes in lipid parameters with empagliflozin in patients with type 2 diabetes. Diabetologie und Stoffwechsel [Internet]. 2016 Apr 19;11(S 01).
12. Briand F, Mayoux E, Brousseau E, Burr N, Urbain I, Costard C, et al. Empagliflozin, via Switching Metabolism Toward Lipid Utilization, Moderately Increases LDL Cholesterol Levels Through Reduced LDL Catabolism. Diabetes. 2016 Apr 5;65(7):2032–8.
13. Liakos A, Karagiannis T, Athanasiadou E, Sarigianni M, Mainou M, Papatheodorou K, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. Diabetes, Obesity and Metabolism. 2014 May 28;16(10):984 – 93.
14. Zhong X, Lai D, Ye Y, Yang X, Yu B, Huang Y. Efficacy and safety of empagliflozin as add - on to metformin for type 2 diabetes: a systematic review and meta-analysis. Eur J Clin Pharmacol [Internet]. 2016;72(6):655– 63.
15. Wazir N, Rehman SU. Efficacy and safety of empagliflozin as add - on therapy in patients of type - 2 diabetes mellitus. J Gandhara Med Dent Sci [Internet]. 2022;9(1):24–7.
16. Storgaard H, Gluud LL, Bennett C, Grøndahl MF, Christensen MB, Knop FK, et al. Benefits and Harms of Sodium - Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta - Analysis. PloS one. 2016 Nov 11;11(11):e0166125–e0166125.
17. Zhang X - L, Zhu Q-Q, Chen Y-H, Li X-L, Chen F, Huang J - A, et al. Cardiovascular Safety, Long-Term Noncardiovascular Safety, and Efficacy of Sodium-Glucose Cotransporter 2 Inhibitors in Patients

With Type 2 Diabetes Mellitus: A Systemic Review and Meta-Analysis With Trial Sequential Analysis. Journal of the American Heart Association. 2018 Jan 20;7(2):e007165

18. Hayashi T, Fukui T, Nakanishi N, Yamamoto S, Tomoyasu M, Osamura A, 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. 2017 Jan 13;16(1):8–8.

19. Chaplin S. ADA updates standards of diabetes care [Internet]. Wiley; 2021.

CONTRIBUTORS
1. Nauman Wazir - Concept & Design; Data Analysis/Interpretation; Drafting Manuscript; Final Approval
2. Shafqat Ur Rehman - Data Acquisition; Critical Revision; Supervision