Real World Study to Evaluate Effect of SGLT2 Inhibitor Dapagliflozin on Markers of Macro and Micro Vascular Complications as add on Treatment in Type 2 Diabetes Patients

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ABSTRACT

Introduction: In patients with type 2 diabetes mellitus, dapagliflozin, the sodium–glucose cotransporter 2 inhibitor has been shown to improve diabetic control and reduce blood pressure. The main objective of the study is to evaluate efficacy of SGLT2 inhibitor dapagliflozin on markers of macro and micro vascular complications as add on treatment in type 2 diabetes patients in real world set up.

Material and methods: This was an observational study done in real world set up. 87 patients were initially selected among whom 5 patients were lost in follow up and 2 patients were excluded as they discontinued the study medicine. 80 patients who received dapagliflozin 10 mg once daily for 24 weeks in addition to metformin 1000 mg and glimepiride 2 mg combination. Changes in both systolic and diastolic blood pressure, HbA1c (Glycated haemoglobin), fasting and postprandial plasma glucose, lipid profile (including Total cholesterol, Triglycerides, LDL and HDL cholesterol), serum creatinine, serum microalbuminuria, eGFR and HOMA IR were noted. All pathological test was executed at NABL accredited lab.

Results: After 24 weeks from baseline there was almost 1.4% reduction in HbA1c. Fasting and post prandial blood glucose was significantly reduced within 24 weeks. HOMA IR was significantly changed. No marked changes were seen in serum creatinine, microalbuminuria and eGFR. There was a favorable reduction in lipid profile.

Conclusion: Dapagliflozin has a very potent glycemic effect and has a significant impact on markers of macro and micro vascular complications as add on treatment in type 2 diabetes patients. In conclusion it can be stated that early addition of dapagliflozin therapy not only helps T2DM patients to achieve their glycemic control but also prevents further macro and micro vascular complications by reducing markers and risk factors.

Keywords: Dapagliflozin, SGLT2 Inhibitor, Markers, Macro and Micro Vascular Complications

INTRODUCTION

Defects in insulin secretion, insulin action, or both leads to develop hyperglycemia which is termed as Diabetes Mellitus (DM) and also characterised as a metabolic disorder. Individuals who have a usually relative (rather than absolute) insulin deficiency and insulin resistance (IR) encompasses as Type 2 Diabetes (T2DM).[1] Both microvascular and macrovascular complications are pathologic hallmark of DM.[2] Various organ systems mainly affecting the eyes, nerves, kidneys, and the heart damage and failure mainly because of chronicity of hyperglycaemia.[3]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors like dapagliflozin, increased glycosuria and lowering of blood glucose by reducing renal glucose reabsorption in the proximal convoluted tubule and also consider as a new class of oral antidiabetic medications.[4] Dapagliflozin was approved by US FDA on 8th January 2014. Several trials have already confirmed the pleiotropic benefits of dapagliflozin.[5-7] Reduction in the blood pressure is an additional beneficial effect of Dapagliflozin, even systolic blood pressure reduced by 5-6 mm Hg which was even comparable to many anti-hypertensive medications.[8] Even Dapagliflozin has documented effect on lipid profile as it reduced high density lipoprotein-cholesterol (HDL-C) (+1.8-4.4% with dapagliflozin vs. 0.4% with placebo) and reduction in triglycerides (-2.4-6.2% vs. -2.1%) with placebo.[9]

Macrovascular complications such as stroke and acute coronary syndromes has been focused on the management of diabetes in recent years. In diabetes both microvascular and macrovascular complications develop simultaneously which have observed by Researchers such as Krentz et al. and Al-Wakeel et al.[10,11] Macro and microvascular complications are rare before puberty which have shown by several cross sectional studies and at least two large longitudinal studies.[12,13] It has already been established that three to fourfold increase in risk in major risk factors such as diabetes like gender and duration of diabetes and age in developing vascular complications.[14] There were several markers which we usually treated in daily practice as markers of detecting progression of macro and micro vascular complications such as systolic and diastolic blood pressure, HbA1c (Glycated haemoglobin), fasting and postprandial plasma glucose, lipid profile (including Total cholesterol, Triglycerides, LDL and HDL cholesterol), serum creatinine, eGFR and HOMA IR.

The main objective of the study was to evaluate efficacy of SGLT2 inhibitor dapagliflozin on markers of macro and micro vascular complications as add on treatment in type 2 diabetes patients in real world set up.

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MATERIAL AND METHODS

This was an observational study done in real world set up. 87 patients were initially selected among whom 5 patients were lost in follow up and 2 patients were excluded as they discontinued the study medicine. 80 patients received dapagliflozin 10 mg once daily for 24 weeks in addition to metformin 1000 mg and glimepiride 2 mg combination. Changes in both systolic and diastolic blood pressure, HbA1c (Glycated haemoglobin), fasting and postprandial plasma glucose, lipid profile (including Total cholesterol, Triglycerides, LDL and HDL cholesterol), serum creatinine, eGFR and HOMA IR were recorded. All pathological test were executed at NABL accredited lab.

In accordance with applicable regulatory requirements, good clinical practices and ethical principles that comply with the Declaration of Helsinki the study was conducted. Prior to participation, written informed consent of all participants were taken along with institutional ethical committee approval.

Graph Pad Prism5; version 5.01 were used to calculate statistical analysis and the results were expressed as mean ± standard deviation (SD). $p < 0.05$ were considered to be statistically significant.

Characteristics	T2DM Patients (N=80)
Age (years)	54.6 ± 12.8
Gender, Male (%)	45 (56%)
Weight (kg)	76.3 ± 9.6
BMI (kg/m2)	29.2 ± 4.0
History of Smoking (%)	28 (35%)
Duration of diabetes (years)	6.8 ± 2.2
Duration of Hypertension (years)	6.1 ± 2.9
SBP (mm/Hg)	136 ± 12
DBP (mm/Hg)	88 ± 8
FPG (mg/dl)	147.8 ± 23
PPG (mg/dl)	279.5 ± 38
HbA1c (%)	8.2 ± 1.2
Total cholesterol (mg/dL)	176.9 ± 25.2
Triglycerides (mg/dL)	162.3 ± 58.4
LDL cholesterol (mg/dL)	109.6 ± 20.2
HDL cholesterol (mg/dL)	44.5 ± 8.5
Creatinine (mg/dl)	0.65 ± 0.2
eGFR	101.7 ± 47.1
Insulin (mU/ml)	14.5 ± 2.9
HOMA IR	5.09 ± 1.1

Table-1: Baseline demographic characteristics of the participants

RESULTS

Overall, 45 (56%) were male, mean age was 54.6 ± 12.8 years, the mean duration of diabetes was 6.8 ± 2.2 years, and the mean duration of hypertension was 6.1 ± 2.9 years. Mean weight was 76.3 ± 9.6 kg and BMI was 29.2 ± 4.0 kg/m2. At inclusion 28 (35%) patients were smoker. Demographic details are listed in table 1.

After 24 weeks from baseline there was almost 1.4% reduction in HbA1c (from 8.2 ± 1.2 to 6.9 ± 0.5, $p< 0.001$). Fasting and and post prandial blood glucose was significantly reduced within 24 weeks ($p< 0.001$). HOMA IR was significantly changed (from 5.09 ± 1.1 to 3.23 ± 1.1; $p< 0.01$). No marked changes in creatinine ($p=0.079$) and eGFR ($p=0.87$) was observed. There was a favorable reduction in lipid profile. Total cholesterol was reduced by almost -21.1 ± 7.3 mg/ dl ($p=0.039$), triglycerides by almost -33.5±4.2 mg/dl ($p=0.042$) and LDL cholesterol by -10.1 ± 4.6 mg/ dl ($p=0.761$), whereas HDL cholesterol was significantly increased by 1.6 ± 0.8 mg/dl ($p< 0.01$). (Table 2)

DISCUSSION

In T2DM subject high insulin resistance (IR) lead to 2.0-fold increase in CVD risk after adjusting several known cardiovascular risk factors, including LDL, triglycerides, high-density lipoprotein, systolic blood pressure, and smoking.[15] Even in this study there was significant reduction in cardiovascular risk factors, including LDL, triglycerides, high-density lipoprotein, systolic blood pressure. Strict glycemic control does limit micro and macrovascular disease and have been demonstrated by several landmark studies such as the United Kingdom Prospective Diabetes Study (UKPDS).[16] By both severities of hyperglycemia and presence of hypertension T2DM patients has been found to

Variables	Baseline	24 Week	Changes	p Value
Weight (kg)	76.3 ± 9.6	75.2 ± 6.2	-1.1 ± 0.9	< 0.01
SBP (mm/Hg)	136 ± 12	122 ± 6	-14 ± 4	< 0.01
DBP (mm/Hg)	88 ± 8	81± 6	-7± 2	< 0.01
FPG (mg/dl)	147.8 ± 23	118.2 ± 16.3	-29.5 ± 10.2	< 0.001
PPG (mg/dl)	279.5 ± 38	185.7 ± 26.8	-93.8 ± 10.3	< 0.001
HbA1c (%)	8.2 ± 1.2	6.9 ± 0.5	-1.3 ± 0.3	< 0.001
Total cholesterol (mg/dL)	176.9 ± 25.2	155.8 ± 29.8	-21.1 ± 7.3	0.039
Triglycerides (mg/dL)	162.3 ± 58.4	128.8 ± 21.8	-33.5 ± 4.2	0.042
LDL cholesterol (mg/dL)	109.6 ± 20.2	99.5 ± 14.8	-10.1 ± 4.6	0.761
HDL cholesterol (mg/dL)	44.5 ± 8.5	46.1 ± 5.4	1.6 ± 0.8	< 0.01
Creatinine (mg/ dl)	0.65 ± 0.2	0.64 ± 0.2	-0.01 ± 0.01	0.079
eGFR	101.7 ± 47.1	102.0 ± 43.8	0.3 ± 0.01	0.87
Insulin (mU/ml)	14.5 ± 2.9	12.5 ± 2.4	-2 ± 1.1	< 0.001
HOMA IR	5.09 ± 1.1	3.23 ± 1.1	-1.86 ± 0.5	< 0.01

Table-2: Change from baseline to 24 week study end point

be at anincreased risk of development of diabetic retinopathy (DR). In the development of DR, significant association between HbA1c, duration of diabetes, body mass index and microalbuminuria already been established (P = 0.001).[17]

Effects of Dapagliflozin on different cardiovascular outcomes has been reported by several randomized controlled trials.[18-21] Taken together, these previous studies indicate that dapagliflozin may reduce cardiovascular mortality. Even in this study cardiovascular risk factors like blood pressure and lipid parameters are reduced significantly. Even it has observed that there is a statistical improvement in HDL ($p< 0.01$).

Serum creatinine and eGFR are risk markers for progression of diabetic nephropathy.[22] Common risk factors such as blood pressure, blood lipids, and glycemic control are observed in the causation of cardiovascular and renal complications. Even in this trial it has observed that 24 weeks treatment with Dapagliflozin results in reduced further deterioration in creatinine level and eGFR rate which advocates renal protection by the drug.

Improvement in microvascular disease can be achieved by strict glycemic control and should be implemented early and maintained for the optimum length of time. Besides glycemic control, good control of lipid parameters and blood pressure are extremely important in macrovascular disease prevention.

The major limitations of this study is the incorporation of small number of patients, nevertheless this study provide useful information for use in daily clinical practice by the clinicians to manage their uncontrolled T2DM patients in a better way.

CONCLUSION

Dapagliflozin has a very potent hypoglycemic effect and has a significant impact on markers of macro and micro vascular complications as add on treatment in type 2 diabetes patients. In conclusion it can be stated that early addition of Dapagliflozin therapy not only helps T2DM patients to achieve their glycemic control but also prevents further macro and micro vascular complications by reducing markers and risk factors.

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REFERENCES

1. Standards of medical care in diabetes-2016: Summary of revisions. Diabetes Care 2016;39:S4-5.
2. Orasanu G, Plutzky J. The pathologic continuum of diabetic vascular disease. J Am Coll Cardiol 2009;53:S35-42.
3. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129–39.
4. Vasilakou D, Karagiannis T,Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013; 159: 262-74.
5. Patel DK, Strong J. The Pleiotropic Effects of Sodium-Glucose Cotransporter-2 Inhibitors: Beyond the Glycemic Benefit. Diabetes Ther. 2019;10:1771-1792.
6. Clegg, Heerspink., et al. Reduction of Cardiovascular Risk and Improved Estimated Glomerular Filtration Rate by SGLT2 Inhibitors, Including Dapagliflozin, Is Consistent Across the Class: An Analysis of the Placebo Arm of EXSCEL. Diabetes Care 2019;42: 318-326.
7. Yamakage H et.al; Effects of dapagliflozin on the serum levels of fibroblast growth factor 21 and myokines and muscle mass in Japanese patients with type 2 diabetes: A randomized, controlled trial. J Diabetes Investig 2020; 11: 653–661.
8. Roumie CL, Liu X, Choma NN, Greevy RA, Hung AM, Grijalva CG, et al. Initiation of sulfonylureas versus metformin is associated with higher blood pressure at one year. Pharmacoepidemiol Drug Saf 2012; 21:515-23.
9. Paisley AN, Yadav R, Younis N, Rao-Balakrishna P, Soran H. Dapagliflozin: a review on efficacy, clinical effectiveness and safety. Expert Opin Investig Drugs 2013; 22: 131-40.
10. Krentz AJ, Clough G, Byrne CD. Interactions between microvascular and macrovascular disease in diabetes: Pathophysiology and therapeutic implications. Diabetes Obes Metab. 2007;9:781–91.
11. Al-Wakeel JS, Hammad D, Al Suwaida A, Mitwalli AH, Memon NA, Sulimani F. Microvascular and macrovascular complications in diabetic nephropathy patients referred to nephrology clinic. Saudi J Kidney Dis Transpl. 2009;20:77–85.
12. Schultz CJ, Konopelska-Bahu T, Dalton RN, et al. Microalbuminuria prevalence varies with age, sex and puberty in children with insulin dependent diabetes followed in a longitudinal study from diagnosis. Diabetes Care 1999;22:495–502.
13. Burger W, Hövener G, Düsterhus R, et al. Prevalence and development of retinopathy in children and adolescents with type-1 (insulin dependent) diabetes mellitus. A longitudinal study. Diabetologia 1986;29:12–22.
14. Barkai L, Vamosi I, Lukacs K. Enhanced progression of urinary albumin excretion in IDDM during puberty. Diabetes Care1998;21:1019–23.
15. Duncan JG. Mitochondrial dysfunction in diabetic cardiomyopathy. Biochim Biophys Acta. 2011;1813:1351–9.
16. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow- up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577–89.
17. Chawla A, Chawla R, Chawla A. Correlation Between Retinopathy Microalbuminuria and Other Modifiable Risk Factors. Presented on American Diabetes Association's 75th Scientific Session; June 5-9; Boston, Massachusetts. 2015.
18. Wiviott SD, Raz I, Bonaca MP, et al. The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. Am Heart J. 2018;200:83-89.
19. Kato ET, Silverman MG, Mosenzon O, et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type

2 Diabetes Mellitus. Circulation. 2019;139:2528-2536.
20. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381:1995-2008.
21. Furtado RHM, Bonaca MP, Raz I, et al. Dapagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Previous Myocardial Infarction. Circulation. 2019;139:2516-2527.
22. Dabla PK. Renal function in diabetic nephropathy. World J Diabetes. 2010;1:48-56.

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