Original Article

A study of SGLT2 inhibitors on levels of plasma atherogenesis biomarkers in diabetes

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Abstract

Background: Diabetes, a chronic metabolic disorder with microvascular and macrovascular complications. Metabolites of hyperglycemia mediates endothelial injury resulting in cascade of atherosclerosis. Atherosclerosis sets up plaque in vessel wall and obliterates the vascular lumen which results in stroke, myocardial infarction, and peripheral vascular disease. Biomarkers like IL-6, hsCRP, fibrinogen are correlated with cardiovascular disease. In our study, we use non-invasive tool to predict the CVD risk like atherogenic index of plasma, Triglyceride to high-density lipoprotein, and triglyceride glucose index. **Methods:** This is a prospective observational study on type 2 diabetes patients on SGLT2 inhibitors attending medicine departments. Data was collected on disease duration, anthropometry, fasting and post prandial glucose, HbA1C, lipid profile at initial visit and after 6 months. Atherosclerosis indices were compared accordingly. **Results:** Among 300 patients enrolled, mean age was 44±6.41 yrs. Triglycerides was 143±4.6mg/dl, after 6 months was123±6.1 with significance($p<0.01$). Low-density Lipoprotein(LDL) was 116 ±12.5mg/dL and after 6 months was 123±17which was significant($p<0.01$). High-density Lipoprotein (HDL) at baseline was 37.9±2.6 mg/dL,at 6 months 49±3.6 with significance ($p<0.01$). Atherogenic index of plasma, baseline was 0.227±0.03, at 6 months was 0.040±0.040 with significance($p<0.01$). Triglyceride glucose index(TyG), baseline was 5±0.05 and 6 months was 4.8±0.04 with significance($p<0.01$). Triglyceride to HDL(TG:HDL), baseline was 3.7±0.2 and at 6 months was 2.56±0.2 with significance ($p<0.01$). **Conclusion:** From our study, we observed that SGLT2 inhibitor shows significant improvement in glycemic profile in addition to lipid profile. SGLT2 inhibitor lowered atherogenic indices.

Keywords: Atherosclerosis, SGLT 2 inhibitors, type 2 diabetes

Introduction

Diabetes mellitus, a chronic metabolic disorder characterized by hyperglycemia, is a major global health concern due to its increasing prevalence and associated complications. One such complication is atherosclerosis, a key pathological process underlying cardiovascular disease (CVD) and a major cause of morbidity and mortality in diabetic patients.[1] Sodium-glucose co-transporter 2 (SGLT2) inhibitors, a class of oral hypoglycemic agents, have emerged as a promising therapeutic option for managing diabetes by promoting glycosuria and reducing hyperglycemia. Beyond their glycemic control effects, emerging evidence suggests that SGLT2 inhibitors may also exert beneficial effects on cardiovascular health through various mechanisms, including reducing body weight, blood pressure, and arterial stiffness.[2]

Recent studies have shown that SGLT2 inhibitors may impact atherogenesis, the process of plaque formation in arteries, by modifying the levels of plasma biomarkers associated with

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atherosclerosis.[3] These biomarkers include inflammatory cytokines, adhesion molecules, lipids, and endothelial function markers, which play crucial roles in the development and progression of atherosclerotic lesions. Understanding the effects of SGLT2 inhibitors on these biomarkers is essential for elucidating their potential cardiovascular benefits beyond glycemic control in diabetic patients.

This study aims to investigate the impact of SGLT2 inhibitors on the levels of plasma atherogenesis biomarkers in patients with diabetes. By examining changes in these biomarkers following treatment with SGLT2 inhibitors, we hope to gain insights into the underlying mechanisms through which these agents may influence atherosclerosis and cardiovascular risk in diabetic patients.[4] In our study, we use non-invasive tools to predict the CVD risk like an atherogenic index of plasma, triglyceride to high-density lipoprotein, and triglyceride glucose index.

Material and Methods

This prospective observational study was conducted on 300 patients with type 2 diabetes patients attending the outpatient and inpatient departments. This study was initiated after obtaining the ethical committee approval [No-DHR-EC/NEW/INST/2021/1618 – 11102022]. We conducted this study over a period of 1 year. Patients who were on SGLT2 inhibitors (Empagliflozin 25 mg OD) were selected and a detailed history, anthropometry, and laboratory analysis were done at baseline and after 6 months of follow-up. Non-invasive tools like atherogenic index of plasma (AIP), triglyceride to high-density lipoprotein ratio, and triglyceride glucose index were calculated at the initial visit and after 6 months. The atherogenic index of plasma (AIP) is defined as the logarithm to the base 10 of the ratio of fasting plasma triglyceride (mg/dL) to HDL (mg/dL) [log10(TG/HDL)]. The triglyceride glucose index was calculated as the natural logarithm of the product of plasma glucose and triglycerides, using the formula Ln (TG [mg/dL] × glucose [mg/dL]/2).

Inclusion criteria

Patients with age > 35 yrs, all patients who are on SGLT2 inhibitors as an add-on therapy are included in the study.

Exclusion criteria

Patients with eGFR < 45 ml/min, type 1 diabetes, woman in pregnancy or lactation, active genitourinary infections, coronary artery disease, cerebrovascular disease, on anti-lipidemic drugs, peripheral vascular disease, diabetic ulcer, allergic or intolerant to SGLT2 inhibitors are not included in the study.

Statistical analysis

The data collected during the study were formulated into a master chart using Microsoft Office Excel, and statistical analysis was performed using the statistical software package SPSS V.17 for Windows. Frequencies, range, mean, standard deviation, and '*p*' values were calculated using Student's *t*-test. Statistical significance was set at $P < 0.05$.

Table 1: Baseline characteristics of the study population

Variable	Frequency	Percentage
Age group (years)		
<40	5	19
41–50	108	36
51–60	72	24
61–70	30	10
>71	33	11
Sex		
Male	164	54.6
Female	136	45.2
BMI		
19–25	240	80
25.1–30	36	12
30.1–35	24	8

Table 2: Laboratory parameter and indices of the study population

Variable	Baseline Mean±SD	At 6 months Mean±SD	*P*
Fasting blood glucose	156±16 mg/dL	134.3±8 mg/dL	0.01
Triglycerides	143±4.6 mg/dL	123±6.1 mg/dL	0.01
Low-density lipoprotein (LDL)	116±12.5 mg/dL	123±17 mg/dL	0.01
High-density lipoprotein (HDL)	37.9±2.6 mg/dL	49±3.6 mg/dL	0.01
Atherogenic index of plasma (AIP)	0.227±0.03	0.040±0.040	0.01
Triglyceride glucose index (TyG)	5±0.05	4.8±0.04	0.01
Triglyceride to high-density lipoprotein (TG: HDL)	3.7±0.2	2.56±0.2	0.01

Results

In our study, the majority of the patients are in the age group of 40-50 yrs (36%) with the least frequency among 60-70 yrs (10%). There is a male predominance of 54.6% and a female of 45.2%. The majority of the patients had with BMI of 19-25 (80%), a BMI of 25–30 (12%), and a BMI of 30–35 (8%) as mentioned in Table 1.

The mean fasting blood sugar of 156 ± 16 mg/dL and post-prandial blood glucose of 253.4 ± 20 mg/dL. The triglycerides were 143 ± 4.6 mg/dL, Low-density Lipoprotein (LDL) was 116 ± 12.5 mg/dL, and the high-density Lipoprotein (HDL) at baseline was 37.9 ± 2.6 mg/dL. On the follow-up after 6 months, the laboratory was done.

The triglycerides were 143 ± 4.6 mg/dL, and after 6 months the mean was123 ± 6.1, which was significant ($P < 0.01$), as mentioned in Table 2. The Low-density Lipoprotein (LDL) was 116 ± 12.5 mg/dL, and after 6 months the mean was 123 ± 17, which was significant ($P < 0.01$). The High-density Lipoprotein (HDL) at baseline was 37.9 ± 2.6 mg/dL and at 6 months was 49 ± 3.6 with significance ($P < 0.01$). The

atherogenic index of plasma at baseline was 0.227 ± 0.03 and at 6 months was 0.040 ± 0.040 with significance ($P < 0.01$). Triglyceride glucose index (TyG) at baseline was 5 ± 0.05 and at 6 months was 4.8 ± 0.04 with significance ($P < 0.01$). Triglyceride to high-density lipoprotein (TG: HDL) at baseline was 3.7 ± 0.2 and at 6 months was 2.56 ± 0.2 with significance ($P < 0.01$).

Discussion

Diabetes causes a dysfunctional metabolic state that affects the arteries, which may lead to atherosclerosis and changes in the function of the endothelium, smooth muscle, and platelets. In diabetes, nitric oxide-mediated vasodilation is inhibited and increases the reactive oxygen species.[5] Besides changes in soluble coagulation and fibrinolytic factors, endothelial cells in diabetes increase the synthesis of tissue factors.[6] Vascular smooth muscle atherogenic activity is due to elevated levels of endothelin and angiotensin. Glycation of LDL was found significantly increased in diabetic patients compared with normal subjects, even in the presence of good glycemic control.[7] Glycation of LDL may alter their structure sufficiently to render them immunogenic and atherogenic, which highlights the fact that non-enzymatic glycation of lipoproteins in the accelerated development of atherosclerosis in diabetic patients. Impaired platelet function plays a role in atherogenesis along with endothelial cell dysfunction.

Hyperglycemia increases the NADPH oxidase activity and decreases the eNOS, which induces endothelial dysfunction and accelerates atherosclerosis.[8] Inflammation milieu due to raised cytokines like IL1, IL6 18, and TNFα contributes to atherosclerosis. Decreased autophagy as a result of increased mTOR (mammalian target of rapamycin) contributes to the progression of atherosclerosis.[9]

Our current study established the efficacy of SGLT 2 inhibitors in reducing the atherogenesis biomarkers, as evidenced by significant changes in the atherogenic index of plasma, triglyceride glucose index, and triglyceride to high-density lipoprotein. Eren Gürkan conducted a study on the effects of dapagliflozin on serum low-density lipoprotein cholesterol and triglyceride levels. Besides showing improvement in glycemic status and body weight, there was a significant decrease in triglycerides as observed in our study.[10] Cha SA *et al.*[11] compared the effect of DPP4 inhibitors and SGLT2 inhibitors on lipid profile in patients with type 2 diabetes. He observed that SGLT2 inhibitor was associated with a significant increase in HDL-C and LDL-C. Shi FH *et al.*[12] reported an increase in HDL in diabetes patients after 24 weeks of treatment with SGLT2 inhibitors. Fadini *et al.*[13] illustrated that for patients with diabetes, 12 weeks of dapagliflozin treatment affected HDL cholesterol; nevertheless, it decreased the cholesterol efflux from macrophages. However, Bosch *et al.*[14] demonstrated that empagliflozin had n significant effect on total cholesterol, HDL, or LDL in type diabetes.

In our study, the Low-density Lipoprotein (LDL) was 116 ± 12.5 mg/dL and after 6 months the mean was 123 ± 17, which was significant ($P < 0.01$). Schernthaner *et al.*[15] demonstrated that after 52 weeks of treatment, canagliflozin increased LDL by 11.7% among patients with type 2 diabetes. Basu *et al.*[16] demonstrated that canagliflozin increased the circulating levels of triglycerides, LDL, and total cholesterol, which was due to increased activity of lipoprotein lipase, decreased post-prandial lipemia, and faster clearance of VLDL from the bloodstream. Animal studies conducted by Osataphan S *et al.*[17] demonstrated that SGLT 2 inhibited the genes involved in cholesterol uptake and synthesis.

Limitations

This is a single-center cross-sectional observational study, and the findings of the study may not be generalizable to other populations or settings, particularly, if the sample is not representative. Multiple studies in varied ethnic backgrounds can help to have a better understanding of the disease.

Conclusion

From our study, we observed that the SGLT2 inhibitor shows a significant improvement in glycemic profile in addition to lipid profile. SGLT2 inhibitor lowered atherogenic indices significantly and can conclude that this drug is efficient in the prevention of macrovascular complications in diabetes.

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Conflicts of interest

There are no conflicts of interest.

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