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COMPARISON OF GLYCEMIC CONTROL ACTIVITY OF SGLT2 INHIBITORS AND SULPHONYLUREAS IN PATIENTS OF IHD

Original Research

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ABSTRACT

Background: The prevalence of Diabetes mellitus (DM) has escalated in the previous decades and is among the major risk factors for developing cardiovascular diseases.1,2 Multiple factors play role in progression of DM towards micro and macrovascular complications. However, poor glycemic control is a main contributor towards the adverse disease outcomes and has been of prime importance in decision making regarding antidiabetic medications.

Methodology: It was a longitudinal cross-sectional study conducted in CMH Jhelum using non-probability convenient sampling technique. Patients having DM and IHD for atleast 1year and with inadequate glycemic control with metformin were selected and analyzed according to demographic details, duration of DM & IHD, therapy group (SGLT2 inhibitors/SU), dosage regimen, incidence of hypoglycemia, comorbidities, history of coronary intervention, baseline and 3-monthly fasting and post-prandial glucose, HbA1c and metabolic profile. Chi square test was applied to find significant difference between both groups and p-value of <0.05 was considered significant.

Results: Among total of 70 patients, 35 patients were divided into each group (Sulphonylureas vs SGLT inhibitors). Both groups had comparable baseline profiles which included gender [males: 17(48.57%) vs 16(45.71%), females: 18(51.43%) vs 19(54.29%)], duration of diabetes (8.37 ± 2.59 vs 8.86 ± 2.43 years, p=0.417) and IHD (7.63 ± 2.68 vs. 7.46 ± 2.52 years, p=0.854), history of coronary intervention (48.57% vs. 54.29%, p=0.632), hypoglycemia (34.29% vs. 48.57%, p=0.225), hypertension (51.43% vs. 34.29%, p=0.147), and dyslipidemia (48.57% vs. 45.71%, p=0.811). Comparison of both groups in glycemic control activity showed almost comparable reduction in fasting blood glucose in both groups ((132.20±19.79 vs 138.69±18.56, p-value=0.143) at 3-monthly follow-up from baseline (159.80±19.52 vs 161.74±18.57, p-value=0.778). However, there was significant difference in reduction in post-prandial glucose (169.40±20.09 vs 159.43±21.45, p-value 0.052) from baseline (198.31±19.71 vs 196.91±21.52, p-value=-0.733) and HbA1c (7.49±0.63 vs 7.05±0.64, p-value=0.006) from baseline (8.26±0.61 vs 8.09±0.59, p-value=0.212) at 3-monthly follow-up.

Conclusion: SGLT2 inhibitors have greater impact in reducing HbA1c and post-prandial blood glucose as compared to SU but further research is needed to elaborate this comparison.

INTRODUCTION

The prevalence of Diabetes mellitus (DM) has escalated in the previous decades and is among the major risk factors for developing cardiovascular diseases.1,2 Multiple factors play a role in progression of DM towards micro and macrovascular complications. However, poor glycemic control is a main contributor towards the adverse disease outcomes and has been of prime importance in decision making regarding antidiabetic medications.3 Cochrane review in 2014 suggested fewer cardiovascular side effects in diabetic patients treated with Sulphonylureas (SU) as compared to those with Metformin.4 Meanwhile recent studies have favored the use of sodium glucose co-transporter 2 (SGLT2) inhibitors in patients with established coronary artery disease.5,6 However the comparative data between glycemic control efficacy of SGLT2 inhibitors and SU is limited.

SGLT2 inhibitors and SU are often used as an add on therapy in patients with uncontrolled DM already using Metformin and in some cases as monotherapy as well.7 SGLT2 inhibitors lower glucose level by inhibiting glucose reabsorption from proximal renal tubules causing glycosuria. They have lower risk of hypoglycemia but are associated with urinary tract infections, euglycemic ketoacidosis and hypotension.7,8 In addition to DM, SGLT2 inhibitors have a promising role in heart failure (HF) as they reduce hospitalization and also have mortality benefit.2,7,9,10 SU causes closure of potassium channels on pancreatic beta cells and increase insulin release. It is associated with increased risk of hypoglycemia and weight gain.4

Literature on comparative effectiveness of these two oral antidiabetic drugs in patients of ischemic heart disease (IHD) in population of Pakistan is lacking. Therefore, the rationale of this study is to compare the glycemic control activity of these two drugs and associated factors in patients with established IHD.

METHODOLOGY:

It was a longitudinal cross-sectional study conducted in Medical Outdoor department Combined Military Hospital (CMH) Jhelum, Pakistan from August 2024 to January 2025. Sample population was randomly selected using non-probability convenient sampling technique.

Inclusion criteria:

All those individuals were included in the study who had diagnosed DM for atleast 1 year, diagnosed IHD for atleast 1 year, whose glycemic control was poor on optimal dosage of metformin and without history of CKD.

DATA COLLECTION:

After taking informed consent patients matching the characteristics of inclusion criteria were categorized according to demographic details (age, gender, BMI), duration of DM, duration of IHD, therapy group (SGLT2 inhibitors/SU), dosage regimen, incidence of hypoglycemia, comorbidities (hypertension & dyslipidemia), and history of coronary intervention. Baseline fasting blood glucose (FBS), random blood glucose (RBS), glycosylated hemoglobin (HbA1c), serum ALT levels, serum creatinine (Cr) and total cholesterol was documented on initial visit. Patients were then called for follow-up after 3 months with regular ambulatory fasting and post prandial glucose monitoring using home-based glucometer. 3-monthly levels of HbA1c, serum creatinine, BMI, ALT and total cholesterol were also documented.

DATA ANALYSIS:

Data was analyzed using SPSS version 25. Frequency tables were used for categorical variables. Bar graph was used for comparison of variables. To find the significant difference between both groups of drugs for different variables chi square test was applied and p value of <0.05 was considered significant.

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ETHICAL APPROVAL:

Ethical approval was taken from the ethical committee of CMH Jhelum duly signed by the Head of Medicine Department.

RESULTS:

Baseline characteristics are given in Table 1 which revealed that both groups were well-matched in terms of age (Sulphonylureas: 59.91 ± 6.07 years; SGLT2 inhibitors: 58.66 ± 5.68 years, p=0.337), gender distribution (male: 48.57% vs. 45.71%, p=0.811), and BMI (28.31 ± 2.48 vs. 29.00 ± 2.67, p=0.276). The duration of diabetes (8.37 ± 2.59 vs. 8.86 ± 2.43 years, p=0.417) and IHD (7.63 ± 2.68 vs. 7.46 ± 2.52 years, p=0.854) were also similar between groups. Comorbidities, including a history of coronary intervention (48.57% vs. 54.29%, p=0.632), hypoglycemia (34.29% vs. 48.57%, p=0.225), hypertension (51.43% vs. 34.29%, p=0.147), and dyslipidemia (48.57% vs. 45.71%, p=0.811), showed no significant differences, confirming comparable baseline profiles.

Comparison between both groups at baseline and at 3-monthly follow-up period is given in Table 2 and Figure 1. At baseline, metabolic parameters showed no significant differences between groups. Fasting glucose levels were 159.80 ± 19.52 mg/dL in the Sulphonylurea group versus 161.74 ± 18.57 mg/dL in the SGLT2 inhibitor group (p-value=0.778), while post-prandial glucose levels were 198.31 ± 19.71 mg/dL and 196.91 ± 21.52 mg/dL respectively (p-value=0.733). HbA1c was comparable (8.26 ± 0.61% vs. 8.09 ± 0.59%, p-value=0.212). Renal function markers, including serum urea (30.31 ± 6.27 vs. 31.54 ± 6.19 mg/dL, p-value=0.410) and creatinine (1.10 ± 0.18 vs. 1.05 ± 0.19 mg/dL, p-value=0.310), were similar, as were liver enzymes (ALT: 30.51 ± 6.28 vs. 29.66 ± 6.52 U/L, p-value=0.613) and lipid profiles (total cholesterol: 181.71 ± 21.32 vs. 189.03 ± 21.60 mg/dL, p-value=0.180). Baseline body weight did not differ significantly (85.51 ± 3.27 vs. 84.57 ± 2.95 kg, p-value=0.228). At the 3-month follow-up, both groups exhibited reductions in fasting glucose, post-prandial glucose, and HbA1c levels. However, the SGLT2 inhibitor group demonstrated a statistically significant greater reduction in post-prandial glucose (p-value=0.052) and HbA1c (p-value=0.006) compared to the Sulphonylurea group. Notably, serum creatinine levels increased significantly in the SGLT2 inhibitor group (p-value<0.001), suggesting a potential impact on renal function. Body weight decreased slightly in the SGLT2 inhibitor group (p-value=0.012), while it increased marginally in the Sulphonylurea group. No significant differences were observed in serum urea, ALT, or total cholesterol levels between the groups (all p-values > 0.05).

Table-1: Patients characersitics

		Sulphonyl ureas	**SGL2 inhibitors**	**p-value**
		35	**35**	
Age		**59.91±6.07**	**58.66±5.68**	**0.337**
Gender	Male	17(48.57%)	16(45.71%)	0.811
	Female	18(51.43%)	19(54.29%)	
BMI		28.31±2.48	29.00±2.67	0.276
Duration of DM		8.37±2.59	8.86±2.43	0.417
Duration of IHD		7.63±2.68	7.46±2.52	0.854
History of coronary intervention		17(48.57%)	19(54.29%)	0.632
History of Hypoglycemia		12(34.29%)	17(48.57%)	0.225
History of Hypertension		18(51.43%)	12(34.29%)	0.147
History of dyslipidemia		17(48.57%)	16(45.71%)	0.811

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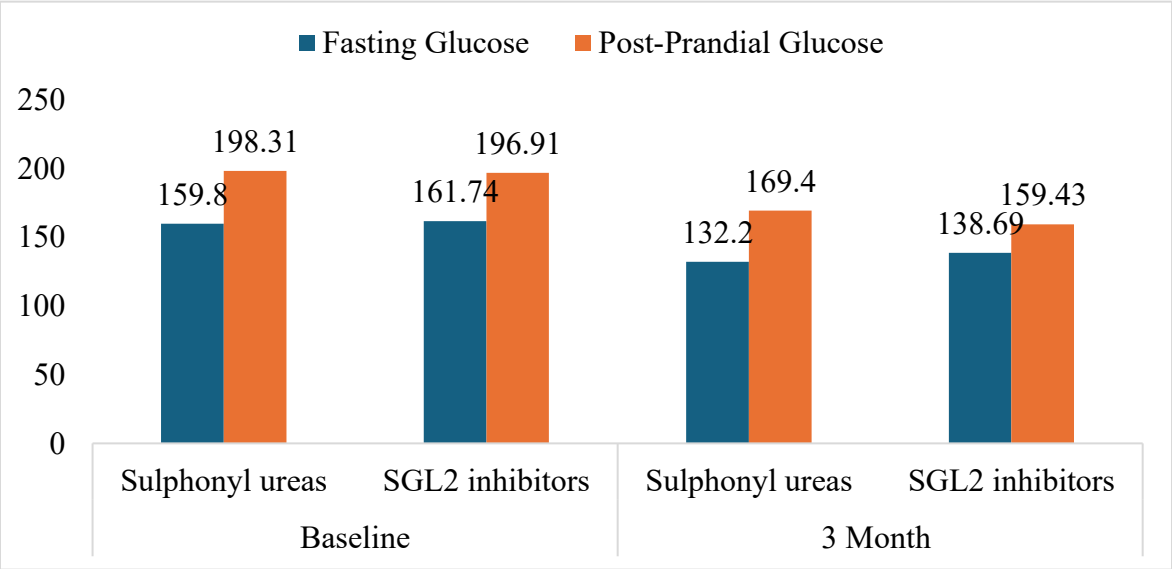
Table-2: Comparison Of Between Groups at Baseline And At 3rd Month Post Treatment

	Baseline			3rd Month		
	Sulphonyl ureas	**SGL2 inhibitors**	**p-value**	**Sulphonyl ureas**	**SGL2 inhibitors**	**p-value**
Fasting Glucose	159.80±19.52	161.74±18.57	0.778	132.20±19.79	138.69±18.56	0.143
Post-Prandial Glucose	198.31±19.71	196.91±21.52	0.733	169.40±20.09	159.43±21.45	0.052*
HbA1c	8.26±0.61	8.09±0.59	0.212	7.49±0.63	7.05±0.64	0.006*
Serum Urea	30.31±6.27	31.54±6.19	0.410	34.06±6.06	35.31±6.32	0.430*
Serum Creatinine	1.10±0.18	1.05±0.19	0.310	1.12±0.18	1.34±0.19	<0.001*
Serum ALT	30.51±6.28	29.66±6.52	0.613	28.60±6.55	28.17±6.56	0.874
Total Cholesterol	181.71±21.32	189.03±21.60	0.180	169.11±20.96	177.37±21.88	0.114
Body Weight	85.51±3.27	84.57±2.95	0.228	86.13±3.24	84.20±2.84	0.012*

Comparison of Fasting Glucose level and Post-Prandial Glucose level between groups



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DISCUSSION:

Achieving adequate glycemic control is essential for preventing and controlling microvascular as well as macrovascular complications in established coronary artery disease.[11,12] Many treatment options are available with metformin being opted as a first line oral hypoglycemic drug followed by second line oral hypoglycemics such as SU, SGLT2 inhibitors, DPP4 inhibitors and GLP1 analogues.[13]

Factors like cardiovascular disease, cost effectiveness, hypoglycemia and evidence of target organ damage play important role in choosing second line antidiabetic drugs for achieving the glycemic control. Trials have shown additional mortality benefits of SGLT2 inhibitors in patients of heart failure other than glycemic control.[14] European society of Cardiology also favors use of SGLT2 inhibitors as second line drug of choice in patients with high CVD risk. One study in USA compared the 2 drugs in discussion for all-cause mortality and SGLT2 inhibitors were concluded to be better in terms of improving all-cause mortality.[7] Considering the cost effectiveness of antidiabetic drugs, SU has higher therapeutic cost effectiveness as compared to others but in long-term perspective of preventing diabetes related complications, hypoglycemic incidence and weight gain, SGLT2 inhibitors have better long-term overall cost-effectiveness. Still economical therapeutic cost and potent glycemic control efficacy of SU are main factors for these drugs to be opted after metformin as 2nd line antidiabetic drugs in developing world.[15,16]

Our study was aimed at the comparison of SU and SGLT2 in achieving glycemic control in IHD. The response was monitored with 3 monthly follow-up. Our results showed no significant difference in both groups in reducing fasting blood glucose after a 3-month follow-up period and both had rather similar efficacy in this regard. This was in contrast to the results of a metanalysis conducted by Ze Chen et al. which showed greater reduction in fasting blood glucose with SGLT2 inhibitors as compared to SU.[17] The difference might be due to sample size variation, different study settings and variable population lifestyle. However, SGLT2 inhibitors showed superior response to SU in reducing mean post prandial glucose and HbA1c at 3-month follow up which is comparable with a cohort study conducted in UK which showed a difference of 4 mmol greater reduction in HbA1c with SGLT2 inhibitors at 12-week follow-up.[18] A meta-analyses of 7 articles conducted by Cokro et al. showed different results from our study having no significant difference among both groups in reducing HbA1c in Asia. These discrepancies in results are main reason for researchers to study these drugs for many years.[19] Other effects of these drugs were also monitored and followed upon. Both groups did not alter the aminotransferase liver enzyme much to be considered significant. Total cholesterol was reduced in both groups but there was no significant difference. SGLT2 inhibitors altered serum creatinine levels significantly with avg rise of about 0.3mg/dl from baseline as compared to SU in which case serum creatinine levels remained almost static after 3 months. But the creatinine levels still remained within the normal range and no adverse renal outcome was encountered. A study conducted by Emre et al. also founded the rise in creatinine levels with SGLT2 inhibitors.[20] Overall data has shown protective effect of SGLT2 inhibitors on kidneys with eGFR>30ml/min owing to diuretic effect and reduction in glucose load in proximal tubule.[21]

Our research is unique in this respect that it shows the direct comparison of glycemic control activity of these 2 drugs along with impact on other factors in IHD patients, the data of which is still under study and this will be a useful addition to overall data in this regard. However, there are certain limitations to our study. Firstly, sample size was small. Secondly, population of a single hospital was studied. Further studies are needed to be conducted with larger set of populations with repeated and longer follow-ups for better understanding in selection of second line antidiabetic drugs and for achieving effective glycemic control with reduction in cardiovascular adverse effects.

CONCLUSION:

Both SGLT2 inhibitors and SU have effective antidiabetic ability and have almost similar impact on fasting blood glucose but SGLT2 inhibitors have greater impact in reducing HbA1c and post-prandial blood glucose.

AUTHOR CONTRIBUTION

Author	Contribution
Zaboor Ahmed*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Waheed Ahmed	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Farah Rao	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Brigadier Abid Javaid Randhawa	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Major Muhammad Usman Khan	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Major Syed Haider Tirmizi	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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