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COMPARISON OF GLYCEMIC CONTROL ACTVITY OF SGLT2 INHIBITORS AND SULPHONYLUREAS IN PATIENTS OF DECOMPENSATED LIVER DISEASE

Original Research

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ABSTRACT

Background: Diabetes mellitus (DM) is a well-established risk factor for worsening structural and biochemical parameters in decompensated chronic liver disease (DCLD), a condition with significant global morbidity and mortality (1,2). Poor glycemic control in DCLD increases the likelihood of complications such as hepatic encephalopathy, gastrointestinal bleeding, and ascites. Achieving optimal glycemic control is essential to slow disease progression, reduce complications, and improve survival outcomes. The selection of appropriate second-line oral antidiabetic drugs (ADDs) in this population remains a matter of clinical debate.

Objective: To compare the efficacy and safety of sulphonylureas (SU) and sodium-glucose co-transporter 2 (SGLT2) inhibitors in achieving glycemic control in patients with DCLD.

Methods: This longitudinal cross-sectional study was conducted at Combined Military Hospital Jhelum from May 2024 to January 2025. Using non-probability convenience sampling, 100 patients with DM and DCLD for at least one-year, inadequate glycemic control on metformin, and no major comorbidities were enrolled. Patients were assigned to either SU (n=50) or SGLT2 inhibitor (n=50) therapy. Baseline and 3-month follow-up assessments included fasting blood glucose (FBG), post-prandial glucose (PPG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, albumin, cholesterol, body weight, and hypoglycemia incidence. Data analysis was performed using SPSS v25 with chi-square test, considering $p<0.05$ as statistically significant.

Results: Baseline characteristics were comparable between SU and SGLT2 groups in age (59.40±9.09 vs 59.96±9.54 years), BMI (29.32±1.53 vs 28.90±2.31 kg/m²), duration of DM (9.70±3.46 vs 10.00±1.93 years), and DCLD (9.16±2.92 vs 9.66±3.10 years). At 3 months, both groups showed reductions in FBG (204.80±25.54 to 175.50±28.32 vs 214.76±26.17 to 169.70±27.88 mg/dL, p=0.305) and PPG (238.02±28.99 to 222.78±25.95 vs 246.10±29.19 to 225.04±25.12 mg/dL, p=0.659), without significant intergroup difference. Hypoglycemia was more frequent in the SU group (16% vs 4%, p=0.046). ALT, albumin, and body weight changes were non-significant between groups.

Conclusion: Both SU and SGLT2 inhibitors demonstrated comparable glycemic control in DCLD, though the lower hypoglycemia incidence with SGLT2 inhibitors suggests a safety advantage in patients with prior hypoglycemia.

Keywords: Albumin, Antidiabetic Agents, Body Weight, Decompensated Liver Cirrhosis, Glycemic Control, Hypoglycemia, Sodium-Glucose Transporter 2 Inhibitors.

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INTRODUCTION

Diabetes mellitus (DM) is a well-recognized risk factor for the deterioration of structural and biochemical parameters in decompensated chronic liver disease (DCLD), a condition that has emerged as a major global health concern (1,2). The coexistence of DM and DCLD increases the likelihood of severe complications, including hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis, while also significantly elevating all-cause mortality (3,4). DCLD itself arises from diverse etiologies such as non-alcoholic steatohepatitis (NASH), chronic hepatitis B and C infections, alcoholic liver disease, and primary hemochromatosis (5,6). In all these conditions, optimal glycemic control remains pivotal for halting disease progression, limiting complications, and improving survival outcomes. Despite global research efforts aimed at reducing diabetes-related mortality in liver disease, the comparative effectiveness of different antidiabetic drug classes in DCLD remains insufficiently explored, particularly at the regional level (7). Among the newer therapeutic options, sodium-glucose co-transporter 2 (SGLT2) inhibitors have gained prominence due to their unique mechanism of action—blocking glucose reabsorption in the renal tubules—and their potential pleiotropic benefits. Evidence suggests that SGLT2 inhibitors may improve hepatic steatosis, reduce inflammation and oxidative stress, lower albuminuria, decrease aminotransferase levels, and possibly reduce the risk of hepatocellular carcinoma (8–11). In contrast, sulphonylureas (SU), long-standing insulin secretagogues often employed as second-line agents after metformin, present a more controversial profile in DCLD due to the risk of hypoglycemia (12,13). Nonetheless, studies have shown that SU use can effectively achieve glycemic control and reduce all-cause mortality in cirrhotic patients, with gliclazide in particular being linked to a reduced risk of hepatocellular carcinoma (14–16). Given the scarcity of comparative data, especially in local clinical contexts, there is a need to investigate the relative effectiveness of SGLT2 inhibitors and sulphonylureas in patients with DCLD. The present study aims to evaluate and compare these two drug classes in achieving glycemic control and to identify associated factors that may significantly influence their therapeutic activity.

METHODS

This longitudinal cross-sectional study was carried out at the Combined Military Hospital, Jhelum, Pakistan, between May 2024 and January 2025. The sample population was recruited using a non-probability convenience sampling technique, and a total of 100 patients were enrolled, with 50 participants allocated to each treatment group. Eligible participants included individuals with a confirmed diagnosis of both diabetes mellitus (DM) and decompensated chronic liver disease (DCLD) for at least one year, demonstrating poor glycemic control despite metformin therapy. Only those without other significant comorbidities such as chronic kidney disease (CKD), ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), or similar systemic illnesses were considered for inclusion. All participants provided written informed consent prior to enrollment. At baseline, demographic and clinical parameters were documented, including age, gender, body mass index (BMI), duration of DM, and duration of DCLD. Participants were then initiated on either sulphonylureas (SU) or sodium-glucose co-transporter 2 (SGLT2) inhibitors as second-line antidiabetic therapy, with allocation described as “random” in the original data but without specification of the randomization process—a methodological limitation that raises potential concerns regarding selection bias. Follow-up was conducted after three months, during which patients maintained an ambulatory-monitored glucose chart that recorded both fasting blood glucose (FBG) and post-prandial blood glucose (PPBG) levels. Clinical assessment included documentation of hypoglycemic episodes and laboratory investigations, namely fasting and post-prandial glucose levels at follow-up, serum urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and total cholesterol. A history of hypertension and dyslipidemia was also recorded. Data analysis was performed using SPSS version 25. Quantitative variables were presented using frequency tables, and associations between variables were examined using the chi-square test. A p-value of less than 0.05 was considered statistically significant. Ethical approval for the study was obtained from the Ethical Committee of Combined Military Hospital, Jhelum and all procedures were conducted in accordance with the Declaration of Helsinki.

RESULTS

The baseline characteristics of patients in the sulphonylurea and SGLT2 inhibitor groups were comparable, with no statistically significant differences in age (59.40 ± 9.09 vs 59.96 ± 9.54 years, p = 0.764), gender distribution (male: 68% vs 62%, p = 0.529), body

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mass index (29.32 ± 1.53 vs 28.90 ± 2.31 kg/m², p = 0.283), or duration of decompensated chronic liver disease (9.16 ± 2.92 vs 9.66 ± 3.10 years, p = 0.409). The duration of diabetes was also similar between the two groups (9.70 ± 3.46 vs 10.00 ± 1.93 years, p = 0.822). Comorbidities such as hypertension (34% vs 30%, p = 0.943) and hyperlipidemia (22% vs 26%) were evenly distributed. At baseline, fasting blood glucose levels were slightly higher in the SGLT2 inhibitor group compared to the sulphonylurea group (214.76 ± 26.17 vs 204.80 ± 25.54 mg/dL, p = 0.057), while post-prandial glucose levels were also higher in the SGLT2 group (246.10 ± 29.19 vs 238.02 ± 28.99 mg/dL, p = 0.168); however, these differences were not statistically significant. After three months of treatment, fasting glucose levels decreased to 169.70 ± 27.88 mg/dL in the SGLT2 inhibitor group and to 175.50 ± 28.32 mg/dL in the sulphonylurea group (p = 0.305). Post-prandial glucose levels fell to 225.04 ± 25.12 mg/dL in the SGLT2 group and 222.78 ± 25.95 mg/dL in the sulphonylurea group (p = 0.659).

Liver function markers demonstrated mild improvements in both groups over the study period. ALT levels decreased from 71.44 ± 16.75 U/L to 63.68 ± 16.56 U/L in the SGLT2 group and from 69.46 ± 18.69 U/L to 59.22 ± 12.95 U/L in the sulphonylurea group (p > 0.05 for both comparisons between groups). AST levels reduced from 61.46 ± 15.65 U/L to 53.36 ± 13.92 U/L in the SGLT2 group and from 57.40 ± 15.06 U/L to 52.00 ± 14.93 U/L in the sulphonylurea group (p = 0.639 at three months). Serum albumin improved slightly in both groups (SGLT2: 2.74 ± 0.17 to 2.90 ± 0.16 g/dL; sulphonylurea: 2.80 ± 0.18 to 2.94 ± 0.15 g/dL), without statistical significance (p > 0.05). Renal parameters remained largely stable, except for serum creatinine, which showed a statistically significant reduction in the SGLT2 inhibitor group compared to the sulphonylurea group at three months (1.15 ± 0.04 vs 1.20 ± 0.04 mg/dL, p < 0.001). Serum urea values exhibited minimal, non-significant changes (p > 0.05). Body weight did not differ significantly between groups at baseline (70.06 ± 8.66 vs 68.84 ± 8.22 kg, p = 0.471) or after treatment (68.94 ± 8.55 vs 69.53 ± 8.30 kg, p = 0.724). Lipid profiles, assessed via total cholesterol, remained unchanged in both groups over the study duration (baseline: SGLT2 200.84 ± 32.85 mg/dL vs SU 199.06 ± 25.69 mg/dL, p = 0.763; 3 months: SGLT2 192.17 ± 32.69 mg/dL vs SU 194.38 ± 26.15 mg/dL, p = 0.709). Hypoglycemic episodes occurred more frequently in the sulphonylurea group compared to the SGLT2 inhibitor group (16% vs 4%, p = 0.046).

Table 1: Baseline characteristics

		Sulphonylureas	**SGL2 inhibitors**	**p-value**
		50	50	
Age		59.40±9.09	59.96±9.54	0.764
Gender	Male	34(68%)	31(62%)	0.529
	Female	16(32%)	19(38%)	
BMI		29.32±1.53	28.90±2.31	0.283
Duration of DCLD		9.16±2.92	9.66±3.10	0.409
Duration of Diabetes		9.70±3.46	10.00±1.93	0.822
Hypertension		17(34%)	15(30%)	0.943
Hyperlipidemia		11(22%)	13(26%)	

Table 2: Comparison of groups at baseline and at 3rd month post treatment

	Baseline			**3rd Month**		
	Sulphonyl ureas	SGL2 inhibitors	p-value	Sulphonyl ureas	SGL2 inhibitors	p-value
	50	50		50	50	
Fasting Glucose	204.80±25.54	214.76±26.17	0.057	175.50±28.32	169.70±27.88	0.305
Post-Prandial Glucose	238.02±28.99	246.10±29.19	0.168	222.78±25.95	225.04±25.12	0.659
Body Weight	68.84±8.22	70.06±8.66	0.471	69.53±8.30	68.94±8.55	0.724
Serum ALT	69.46±18.69	71.44±16.75	0.578	59.22±12.95	63.68±16.56	0.122
Serum AST	57.40±15.06	61.46±15.65	0.189	52.00±14.93	53.36±13.92	0.639
Serum Albumin	2.80±0.18	2.74±0.17	0.127	2.94±0.15	2.90±0.16	0.158
Total Cholesterol	199.06±25.69	200.84±32.85	0.763	194.38±26.15	192.17±32.69	0.709
Serum Urea	20.35±1.12	20.02±1.20	0.173	19.34±1.47	18.92±1.11	0.105
Serum Creatinine	1.19±0.07	1.20±0.06	0.508	1.20±0.04	1.15±0.04	<0.001

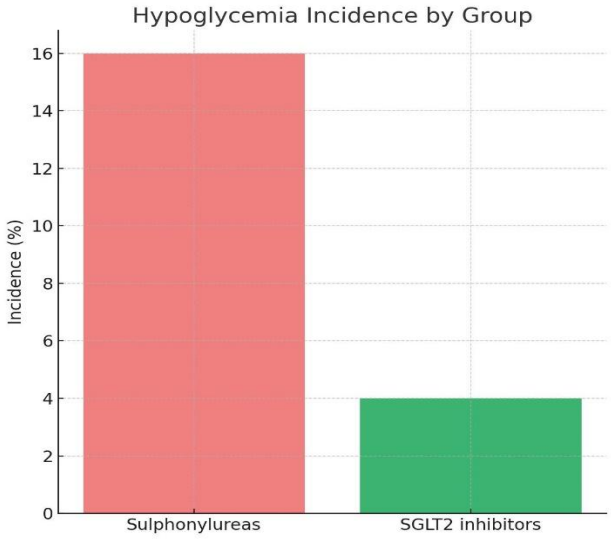

Figure 1 Hypoglycemia Incidence by Group

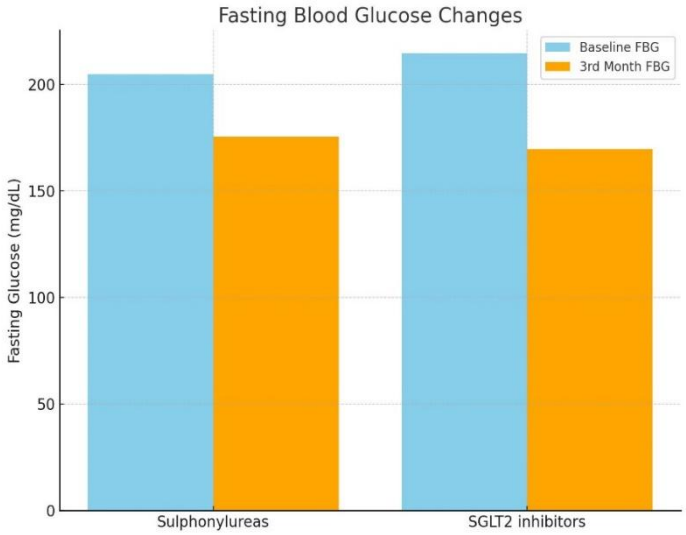

Figure 2 Fasting Blood Glucose Changes

DISCUSSION

Poor glycemic control in individuals with decompensated chronic liver disease (DCLD) is associated with an increased risk of adverse clinical outcomes, including the development of hepatocellular carcinoma (HCC) and other decompensatory complications such as hepatic encephalopathy, upper gastrointestinal bleeding, and ascites (17). Strategies to optimize glycemic control in this population typically include lifestyle modifications and pharmacological therapy, with metformin widely recognized as the first-line oral hypoglycemic agent due to its demonstrated benefits in reducing DCLD-related complications (18,19). However, the selection of an appropriate second-line agent remains a subject of ongoing debate, with multiple drug classes, including sulphonylureas (SU) and sodium-glucose co-transporter 2 (SGLT2) inhibitors, under consideration. Previous studies have indicated that SGLT2 inhibitors are effective in non-alcoholic fatty liver disease (NAFLD), primarily through weight reduction and glycemic control, and may be beneficial in slowing the progression of diabetes-associated hepatic injury towards cirrhosis and HCC (20). Additionally, evidence suggests a potential reduction in hepatic complications among patients with chronic hepatitis B treated with these agents (21). Sulphonylureas, in contrast, are hepatically metabolized and carry a higher risk of hypoglycemia, which can be particularly concerning in patients with impaired hepatic clearance and hypoalbuminemia (18,22). Nevertheless, literature has also shown that SU use in compensated cirrhosis may be associated with reduced all-cause mortality, highlighting their potential utility in selected cases (22).

The present study evaluated the comparative efficacy of SU and SGLT2 inhibitors in achieving glycemic control among patients with DCLD. Over a three-month follow-up, both treatment groups demonstrated comparable reductions in fasting and post-prandial glucose levels, with a more pronounced effect observed on fasting glucose. These findings are consistent with previous randomized controlled trials that have shown similar glucose-lowering capabilities for both drug classes over longer treatment durations (23,24). Reductions in aminotransferases (ALT and AST) were observed in both groups, without significant intergroup differences, aligning with earlier studies assessing the hepatic safety of these agents in chronic liver disease (23,24). Likewise, serum albumin levels showed a modest increase in both groups, though changes were not statistically significant. A notable distinction emerged in the incidence of hypoglycemia, which was higher in the SU group compared to the SGLT2 inhibitor group. This is clinically relevant in the context of DCLD, where altered drug metabolism and hypoalbuminemia can heighten hypoglycemia risk (25). In contrast, body weight remained stable in both groups, differing from earlier findings where SGLT2 inhibitors were associated with weight reduction and SU with weight gain (6,7,23,24). This discrepancy may be attributable to the short study duration, small sample size, or the specific metabolic characteristics of the DCLD population.

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The study offers a unique contribution by directly comparing these two classes of oral antidiabetic drugs in patients with decompensated liver disease, a population for which limited comparative data exists. Previous investigations have primarily focused on NAFLD or compensated cirrhosis, making the present findings an important addition to the literature. The study's strengths include a clearly defined patient cohort and standardized follow-up with objective biochemical monitoring. However, several limitations warrant consideration. The sample size was relatively small, potentially limiting statistical power to detect subtle differences. The follow-up period of three months was short, preventing assessment of longer-term outcomes, including sustained glycemic control, hepatic disease progression, or survival. The lack of randomization details raises the possibility of allocation bias. Additionally, certain potentially informative variables, such as HbA1c trends, inflammatory markers, or detailed stratification by baseline disease severity, were not analyzed. HbA1c was deliberately excluded due to the risk of inaccurate readings in DCLD secondary to anemia and hypersplenism (17), but alternative long-term glycemic markers could have been considered. Future research should incorporate larger, multicenter cohorts with longer follow-up durations to assess not only glycemic and biochemical changes but also clinical endpoints such as rates of hepatic decompensation, HCC development, and mortality. Including broader biochemical and imaging parameters may further clarify the potential extra-glycemic benefits of these drug classes. Such data would help guide more individualized therapeutic decisions for glycemic control in this vulnerable patient population.

CONCLUSION

The findings of this study indicate that both sulphonylureas and SGLT2 inhibitors offer comparable efficacy in achieving glycemic control in patients with decompensated chronic liver disease. However, given the higher risk of hypoglycemia associated with sulphonylureas, careful consideration is warranted when prescribing them, particularly in individuals with a prior history of hypoglycemic episodes. In such cases, SGLT2 inhibitors may represent a safer and more suitable therapeutic option, supporting a more tailored approach to managing diabetes in this high-risk population.

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
Muhammad Usman Khan	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Farah Rao	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Syed Haider Tirmizi	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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