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Beneficial effects of SGLT2 Inhibitors on Fatty Liver in Type 2 Diabetes Mellitus

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ABSTRACT

Objectives: To evaluate the effects of treatment with SGLT 2 inhibitors on fatty liver disease in patients with type 2 diabetes mellitus. **Study design:** Quasi-experimental study. **Place and duration of study:** Department of Medicine, PAF hospital Islamabad from Apr-2024 to Mar-2025. **Methods:** A total of 100 type 2 diabetic patients diagnosed with non-alcoholic fatty liver disease (Grade 1–3) were enrolled and divided into two equal groups. The study group received SGLT2 inhibitor in addition to their existing antidiabetic treatment while controls continued standard antidiabetic treatment. Baseline demographic, anthropometric data, blood glucose and liver enzyme tests were recorded, while the hepatic steatosis was assessed and graded by ultrasound. The primary outcome was the significance of difference in hepatic steatosis grade, while secondary outcomes included significance of difference in liver enzyme levels, glycemic control, waist circumference, and body weight after six months treatment. **Results:** The mean age of patients was 53.26 ± 9.03 years, with males comprising 59% and females 41% of the study population. At 6-month follow-up, significantly more patients (18%) in the study group achieved complete resolution of steatosis (Grade 0) compared to 2% in the control group, with a significant difference in steatosis grade distribution ($\chi^2 = 9.476$, df = 3, p = 0.024). Patients on SGLT2 inhibitors showed significant decreased levels of ALT (p = 0.02), AST (p = 0.02), waist circumference (p = 0.01), body weight (p = 0.02) and HbA1c (p = 0.01) compared to the controls. **Conclusion:** SGLT2 inhibitors show benefits in terms of improved hepatic steatosis, liver enzymes, glycemic control, and anthropometric measures suggesting their potential role in managing the diabetic patients with fatty liver disease.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is marked by excess fat accumulation in the liver when significant alcohol intake is absent and is now recognized as the hepatic manifestation of metabolic syndrome. It is particularly common in individuals with type 2 diabetes mellitus (T2DM), as the international data show a co-existence rate of 70–80%.[1] This co-existence increases insulin resistance, accelerates hepatic steatosis, and enhances the risk of progressive liver disease. The shared pathophysiology of these conditions includes insulin resistance, dyslipidemia, chronic inflammation, and oxidative stress which lead to worsen the overall situation. The high prevalence of coexistence significantly increases the risk of progression and potential for severe outcomes such as high incidence of cardiovascular (CV) disease, liver fibrosis, and mortality. Investigating NAFLD in T2DM thereby becomes crucial for developing targeted, dual-purpose therapeutic strategies.[2,3]

Despite its high prevalence, effective pharmacological interventions for NAFLD in diabetic patients remain limited and the management mainly comprised of lifestyle modifications and weight loss strategies. Traditional therapies for T2DM with coexisting NAFLD often fall short, as they primarily target glucose control without addressing hepatic fat. Conventional agents, like insulin and sulfonylureas (SU), may worsen steatosis by promoting lipogenesis and weight gain. Similarly antidiabetic therapies such as metformin and thiazolidinediones (TZDs) offer only modest benefits for NAFLD, and concerns regarding their long-term safety and efficacy persist.[4,5]

In this scenario, newer treatments are being explored to address the shared mechanisms and work for both metabolic and liver outcomes. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, a recent class of oral antidiabetic (OAD) agents, have appear to offer valuable treatment option for these patients, by not only lowering glycemic levels but also providing metabolic benefits. This class has shown to reduce weight, improve hepatic steatosis and offer CV protection in diabetic patients with fatty liver.[6]

SGLT2 Inhibitors work through an insulin-independent mechanism by blocking glucose reabsorption in the proximal renal tubules, causing glycosuria and reducing blood glucose levels. These medications show promising effects on fatty liver disease (FLD) by acting through multiple pathways including decreased hepatic lipogenesis, enhanced fatty acid oxidation, improved mitochondrial function, and reduced inflammation. SGLT2 Inhibitors have shown to promote favorable body composition changes, visceral fat loss, and improved lipid profiles.[6] Studies have suggested improvements in liver enzymes and hepatic fat content with these drugs including empagliflozin, dapagliflozin, and canagliflozin. These benefits of SGLT2 inhibitors have been demonstrated in randomized trials and imaging studies; however, the findings vary depending on the specific drug used, patient demographics, clinical histories, study durations, and regional differences.[7,8,9]

With an estimated prevalence of 17.1%, Pakistan has a rising burden of T2DM. Due to our sedentary lifestyles and dietary habits, this high prevalence is coupled with increasing rates of NAFLD. Patients in our region often present with more severe insulin resistance and earlier onset of complications, including FLD. Despite this, the data from our local studies for assessing the effect of SGLT2 inhibitors on hepatic parameters in patients with T2 DM are limited.[10]

This study was therefore aimed to find the benefits of SGLT2 Inhibitors on fatty liver in T2 DM patients, utilizing both biochemical and radiological markers, over a six month treatment period. These findings will help to establish the role of SGLT2 inhibitors as dual-purpose agents for diabetic patients with hepatic steatosis, optimizing therapeutic approaches beyond glycemic control.

METHODOLOGY

This Quasi-experimental study was conducted at the Department of Medicine, PAF hospital Islamabad from April 2024 to March 2025 over a period of 1 year after getting approval from ethical committee of the hospital.

Sample size was calculated using WHO sample size calculator for comparing means between two independent groups. Based on a previous study demonstrating mean ALT levels of 39.4 ± 11.9 U/L in the SGLT2 inhibitor group versus 74.4 ± 18.7 U/L in the control group, with an alpha level of 0.05 (two-sided) and power of 90%, the estimated sample size (n)= 5 participants per group.[11] However, to account for potential dropouts and ensure adequate statistical power in real-world clinical practice, we recruited 50 participants per group (total n=100 patients).

A total of 50 patients with established T2DM were enrolled in the study group. Inclusion criteria were set, as age between 18 and 70 years, hemoglobin A1C (HbA1c) levels ranging from 7.0% to 10.0%, and the presence of NAFLD confirmed by abdominal ultrasonography (USG) showing hepatic steatosis (Grade 1–3). All patients were required to be on a stable antidiabetic or metabolic treatment regimen for at least three months prior to enrollment.

Exclusion criteria was set as patients with significant alcohol consumption, other causes of chronic liver disease (such as viral hepatitis B or C, autoimmune hepatitis, or Wilson's disease), estimated glomerular filtration rate (eGFR)<30 mL/min/1.73m^2, history of diabetic ketoacidosis or active malignancy. Patients who had previously used SGLT2 inhibitors within 6 months or patients with severe cardiac, renal, or hepatic dysfunction were also excluded.

Written consent was obtained from the patients before their enrollment.

Participants were allocated into two equal groups of 50 patients each, where patients in the study group received SGLT2 inhibitors (empagliflozin 10-25mg, dapagliflozin 5-10mg, once daily) in addition to their existing antidiabetic therapy (including metformin, insulin and SUs) while the patients in control group (n=50) continued with standard antidiabetic treatment or added any antidiabetic therapy (including metformin, insulin and SUs) except SGLT2 inhibitors for their diabetic control. Treatment allocation was decided by the clinical judgment of attending physician, as per the suggested protocols and routine practices of the institute.

Patients on TZDs and GLP-1 receptor agonists were not included in either group due to their possible independent effects on hepatic steatosis.

Demographic details and anthropometric measurements like BMI and waist circumference (WC) were recorded for all the study participants. Comprehensive clinical assessments and laboratory investigations were then performed for each patient. Biochemical parameters including fasting blood glucose (FBG), hemoglobin A1c (HbA1c), ALT, aspartate aminotransferase (AST), complete lipid profile, and comprehensive liver function tests were investigated at base-line (evaluated through fasting blood samples collected after 12-hour overnight fasting). Abdominal USG examinations were then performed by experienced radiologists, where hepatic steatosis was graded according to standard criteria ranging from Grade 0 (normal) to Grade 3 (severe steatosis) based on echogenicity patterns and hepatorenal contrast.[12] All these assessments were then repeated after 6 months of treatment.

The primary outcome was significance of difference in hepatic steatosis grade, while secondary outcomes included significance of difference in liver enzyme levels, glycemic control, waist circumference (WC), and body weight (BW) after six months treatment in the study group compared to controls.

Data analysis was performed using SPSS version 26.0. Continuous variables (such as ALT, AST, HbA1c, weight) were expressed as mean ± standard deviation and compared between groups using independent t-tests or Mann-Whitney U tests, depending on normality (assessed by Shapiro-Wilk test). Categorical variables (steatosis grades) were analyzed using chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant.

RESULTS

The mean age of patients in this study was 53.26 ± 9.03 years ranging from 36 to 70 years. The percentage of male patients was slightly higher (59%) than the female patients (41%) in overall study population. The base line demographics, anthropometric and clinical findings were comparable for both the groups as shown in Table-I.

Table I

Demographics, anthropometric and clinical findings (n=100)

Demographics, anthropometric and clinical findings		Study group (n=50)	Control group (n=50)	p-value
Age (Mean± SD) years		52.76±9.39	53.76±8.72	0.58
Gender	Male n (%)	32 (64)	27 (54)	0.31
	Female n (%)	18 (36)	23 (46)	
Weight (Mean± SD) Kg		88.02±5.97	86.16±5.14	0.10
Waist circumference (Mean± SD) cm		91.7±3.4	92.68±5.47	0.28
Body mass index (Mean± SD) Kg/m^2		29±2.50	28.58±2	0.36
Duration of diabetes (Mean± SD) years		8.9±2.75	8.16±2.87	0.19
HbA1c (Mean± SD) %		7.84±0.61	8.04±0.67	0.12
ALT (Mean± SD) U L^{-1}		47.38±5.41	48.44±5.17	0.32
AST (Mean± SD) U L^{-1}		43.76±3.14	42.82±2.78	0.12
Steatosis grade	I n (%)	12 (24)	13 (26)	0.87
	II n (%)	28 (56)	29 (58)	
	III n (%)	10 (20)	8 (16)	

The distribution of hepatic steatosis grades on USG at 6 months follow-up showed that SGLT2 inhibitor had significantly improved distribution of steatosis grades, with a notably higher proportion of patients achieving complete resolution of hepatic steatosis (Grade 0) in the study group compared to controls (18% Vs. 2%). The chi-square test revealed a statistically significant association between treatment group and hepatic steatosis grade (χ^2 = 9.476, df = 3, p = 0.024) as shown in Table-II.

Table II

Hepatic steatosis grade on USG at 6 months n=100

Steatosis grade at 6 months follow up	Study group (n=50)	Control group (n=50)	p-value/x^2
0 n (%)	9 (18)	1 (2)	0.02/9.48
I n (%)	19 (38)	15 (30)	
II n (%)	17 (34)	27 (54)	
III n (%)	5 (10)	7 (14)	

Patients on SGLT2 inhibitors showed significant decreased levels of ALT (p = 0.02), AST (p = 0.02), WC (p = 0.01), body weight (p = 0.02) and HbA1c (p = 0.01) compared to the controls as shown in Table-III.

Table III

Assessment of Liver enzymes, glycemic control and anthropometric measurements at 6 months follow up (n=100)

Secondary outcomes	Study group (n=50)	Control group (n=50)	p-value/t-value
ALT (Mean± SD) U L^{-1}	43.76±4.73	46.06±4.57	0.02/2.47
AST (Mean± SD) U L^{-1}	40.02±1.72	41.2±1.75	0.02/2.38
HbA1C (Mean± SD) %	7.52±0.24	7.67±0.33	0.01/2.60
Waist circumference (Mean± SD) cm	89.96±1.84	92.02±4.85	0.01/2.8
Body weight (Mean± SD) Kg	82.88±5.23	85.56±5.64	0.02/2.46

No serious adverse events related to SGLT2 inhibitor were reported during the 6-month study period. Minor side effects included mild genital infections reported in 3 patients (6%) and polyuria reported in 5 patients (10%) in the study group, which were resolved with appropriate management and didn't required discontinuation of treatment.

DISCUSSION

Patients in our study demonstrated significant improvements in hepatic and metabolic parameters with SGLT2 inhibitor therapy. After six months, 18% of the SGLT2 inhibitor group achieved complete resolution of hepatic steatosis (Grade 0) compared to only 2% in controls (χ^2 = 9.476, p = 0.024), highlighting their superior efficacy in reducing liver fat. Additionally, SGLT2 inhibitors led to significant reductions in ALT (p = 0.02), AST (p = 0.02), waist circumference (p = 0.01), body weight (p = 0.02), and HbA1c (p = 0.01). This finding suggested superior efficacy of SGLT2 inhibitors in reducing hepatic fat accumulation and improvement in liver steatosis grades when compared to standard antidiabetic therapy without SGLT2 inhibitors. These findings align with emerging body of evidence during last few years supporting SGLT2 inhibitors as a promising therapeutic option for this high-risk population.

A review by Scheen AJ published in 2019 comprehensively worked on the initial evidence demonstrating the benefits of SGLT2 inhibitors in diabetic patients with NAFLD. The review highlighted the ability of this class to reduce the liver fat content, improve liver enzymes, and potentially lower inflammation and oxidative stress, in addition to their already established CV and renal protective effects.[13]

Building upon these foundational insights, several clinical studies have further explored the impact of SGLT2 inhibitors on NAFLD in diabetic populations. Gameil MA et al. aimed to find the effect of SGLT2 Inhibitors compared to commonly used treatments on the status of fatty liver in diabetic patients. The results showed a significant improvement of the fatty liver index (FLI) with a significant reduction of BW, BMI, WC, ALT, AST, GGT and lipid profile (p<0.001 for all), in SGLT2 inhibitors group in a six months follow up time.[11] Real-world data also supported these findings in a study by Euh W et al. conducted in 765 Korean T2DM patients with NAFLD and demonstrated that this class provide superior benefits compared to other OADs. The SGLT2 inhibitor group achieved significantly greater weight loss (-1.3 kg vs. 0.0 kg at 6 months) and more substantial reductions in ALT levels at 3, 6, and 12 months. SGLT2 inhibitors were thereby found to independently improve liver enzymes, confirming their therapeutic advantage in diabetic patients with established FLD.[14]

In a recent study conducted in Egypt by Amin MA et al., the effect of SGLT2 inhibitors (empagliflozin 10 mg daily) on fatty liver in diabetic patients was evaluated over a follow up period of 24 weeks. Adding empagliflozin to standard treatment significantly reduced liver fat by

13.16% and improved BMI (P < 0.001), blood sugar (p=0.03, and liver enzymes (p=0.01). The findings suggested that SGLT2 inhibitors can be a beneficial addition to treatment for diabetics with FLD.[15] Similar findings were shared in a recently published study in Pakistan by Sajad Q et al. where the effectiveness of empagliflozin (SGLT2 inhibitor) was evaluated in reducing liver fat content and improving metabolic parameters in patients with T 2 DM and FLD. The results demonstrated a significant (12.07%) reduction in liver fat as measured by USG, along with a notable decrease in ALT levels from (38 IU/L to 28 IU/L, p< 0.0001), indicating improved liver health. Additionally, empagliflozin led to a 1.6% reduction in HbA1c (p< 0.0001), highlighting its benefits for blood sugar control.[16]

Further review-based evidence consolidates the therapeutic potential of SGLT2 inhibitors in managing NAFLD. Amjad W et al. in their review focused on the role of SGLT2 Inhibitors and supported the use of SGLT2 inhibitors in managing FLD in diabetic patients. This review demonstrated improved liver function through significant reductions in ALT and AST levels. Although changes in fibrosis and steatosis were not statistically significant in overall results of this review, positive trends were present suggesting a potential therapeutic benefit in NAFLD among T2DM patients.[17] A review conducted by Yaribeygi H et al. also highlighted the potential role of SGLT2 inhibitors in improving liver health in diabetic patients with a higher risk of liver dysfunction. Beyond their well-known glucose-lowering effects, emerging evidence suggested that this class may offer extra-glycemic benefits, including protective effects against FLD and other hepatic complications. This review positioned SGLT2 inhibitors as a valuable treatment option for diabetics with concurrent liver disease.[18]

In short, accumulating evidence from reviews and clinical studies supports the dual benefit of SGLT2 inhibitors in improving both glycemic control and hepatic outcomes in diabetic patients with NAFLD, and position them as a promising therapeutic option in this high-risk population.

Limitations of this study include its lack of randomization, short follow up duration and relatively small sample size, which may restrict the generalizability of these findings. Additionally, the lack of liver biopsy or advanced imaging (e.g., FibroScan) to confirm steatosis grades can affect the precision of our assessment of hepatic fat.

CONCLUSION

SGLT2 inhibitors demonstrate advantages in the management of FLD in T2DM in shape of improvements in hepatic steatosis, liver enzymes, glycemic control, and anthropometric measures. These outcomes point towards the potential of SGLT2 inhibitors as a valuable addition to current treatment regimen addressing both metabolic and hepatic complications. Further long-term studies are suggested in our local population to validate these results and explore broader clinical applications.

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