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EFFECTS OF SGLT2 INHIBITORS ON FIB-4 INDEX IN TYPE 2 DIABETIC PATIENTS WITH MASLD: A RETROSPECTIVE CASE-CONTROL STUDY

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) with metabolic dysfunction-associated steatotic liver disease (MASLD) accelerates liver fibrosis. Sodium-glucose co-transporter 2 (SGLT2) inhibitors may have hepatoprotective effects, but their impact on fibrosis markers remains unclear. This study evaluates their effects on FIB-4 index in T2DM and MASLD.

Methods: This retrospective cohort study analyzed clinical data from adult patients with T2DM and MASLD treated between 2022 and 2024. Patients were categorized into SGLT2 inhibitor users and controls. Changes in n FIB-4 index, liver function tests, and metabolic markers were assessed.

Results: The study included 176 participants (73 receiving SGLT2 inhibitors, 103 in the control group). The mean FIB-4 index decreased in the SGLT2 inhibitor group (1.27 ± 0.72 to 1.09 ± 0.56, p = 0.050), whereas it increased in the control group (1.54 ± 1.54 to 1.69 ± 2.47, p = 0.399). Liver function tests showed minor changes, with ALT decreasing in both groups (SGLT2I: 29.73 ± 21.64 to 29.24 ± 32.62 U/L, p = 0.906; control: 42.48 ± 94.30 to 30.65 ± 34.75 U/L, p = 0.221).

Conclusion: SGLT2 inhibitors may help attenuate liver fibrosis progression in T2DM and MASLD. Their combination with other antidiabetic agents enhances benefits. Further prospective studies are needed to confirm these findings and assess long-term liver outcomes.

Keywords: SGLT2 inhibitors, liver fibrosis, Fibrosis-4 index, MASLD, combination therapy

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, leading to persistent hyperglycemia [1]. Globally, the prevalence of T2DM has been rising, posing significant health challenges [2] A common comorbidity associated with T2DM is Metabolic dysfunction-associated steatotic liver disease (MASLD), previously referred to as NAFLD, which encompasses a spectrum of liver conditions ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, and potentially cirrhosis [3]. The coexistence of T2DM and MASLD not only exacerbates liver-related morbidity but also increases the risk of cardiovascular diseases, thereby compounding the overall disease burden [4] SGLT2 inhibitors are a class of oral antidiabetic agents that lower blood glucose levels by inhibiting renal glucose reabsorption, thereby promoting glycosuria [5]. Beyond their glucose-lowering effects, SGLT2 inhibitors have demonstrated additional benefits, including weight reduction, blood pressure lowering, and favorable cardiovascular and renal outcomes [6]. Recent studies have suggested that SGLT2 inhibitors may also exert beneficial effects on liver function in patients with T2DM and MASLD. For instance, a study by Kuchay et al.[7] reported significant reductions in liver fat content and improvements in liver enzymes among patients treated with empagliflozin. The Fibrosis-4 (FIB-4) index is a non-invasive scoring system developed to estimate the degree of liver fibrosis in individuals with liver diseases [8]. It incorporates readily available clinical parameters, including age, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count. Due to its simplicity and cost-effectiveness, the FIB-4 index has gained widespread acceptance in clinical practice as a tool for assessing liver fibrosis, particularly in patients with MASLD and T2DM [9].

METHODS

Study Design and Population:

This research adopts a retrospective cohort study design to evaluate the therapeutic potential of sodium-glucose cotransporter-2 (SGLT2) inhibitors in managing T2DM and MASLD. The study investigates the impact of SGLT2 inhibitors on liver fibrosis using the Fibrosis-4 (FIB-4) index as the primary non-invasive assessment tool. The retrospective design allows for the analysis of previously collected real-world data, ensuring cost-effectiveness and feasibility.

Study Population:

This study included adults aged 18–70 years with MASLD complicated by T2DM, who were receiving SGLT2 inhibitors and other antidiabetic agents. Participants had imaging-confirmed hepatic steatosis and elevated liver enzymes (ALT, AST) without secondary causes of steatosis. The diagnosis of T2DM was confirmed through clinical and laboratory findings, and eligible patients had baseline FIB-4 index scores within the mild to moderate liver fibrosis range (1.3–3.25).Patients were excluded if they had a history of alcohol abuse (≥30 g/day for men, ≥20 g/day for women), alcohol-related liver disease, significant renal

impairment (eGFR <45 mL/min/1.73 m^2), or were classified as Child-Pugh Class C. Those with active malignancies or other confounding comorbidities were also excluded. The primary outcome measure was the change in the Fibrosis-4 (FIB-4) index, while secondary outcomes included changes in the liver function parameters (ALT, AST), and metabolic markers (BMI, random blood glucose). This study adhered to strict ethical guidelines, including the Declaration of Helsinki and local research regulations. The Institutional Review Board (IRB) of the participating hospital reviewed and approved the study protocol (Approval Number: **[2025054K]**) to ensure compliance with ethical and scientific standards.

Statistical Analysis:

Descriptive statistics summarized baseline characteristics. Continuous variables were expressed as means with standard deviations (SD) or medians with interquartile ranges (IQR). Paired t-tests were used for normally distributed variables, while Wilcoxon signed-rank tests analyzed non-normally distributed variables. A p-value <0.05 was considered statistically significant.

RESULTS

Demographic, Anthropometric and Clinical characteristics:

At baseline, the demographic and anthropometric parameters of patients in the SGLT2 inhibitor (SGLT2 I) group and the control group were assessed. The mean age of participants was 55.85 years in the SGLT2 I group and 54.65 years in the control group. The average weight was 74.79 kg in the SGLT2 I group and 67.41 kg in the control group. Similarly, the body mass index (BMI) was recorded at 26.64 kg/m^2 in the SGLT2 I group and 25.68 kg/m^2 in the control group.Platelet (PLT) levels, which play a vital role in blood clotting and vascular function, were measured at 224.43 × 10^9/L in the SGLT2 inhibitor (SGLT2 I) group and 211.40 × 10^9/L in the control group. In the SGLT2 inhibitor (SGLT2 I) group, ALT levels were measured at 29.73 U/L, and AST levels were recorded at 24.93 U/L. GGT level was 38.93 U/L in the SGLT2i group and 36.57 U/L in the control group.While the glucose level was 10.37 mmol/L in the SGLT2i group and 10.57 mmol/L in the control group.

Outcome at Follow-up:

At follow-up, changes in demographic and anthropometric parameters were observed in both groups. The mean age increased to 57.08 years in the SGLT2 inhibitor (SGLT2 I) group and 55.78 years in the control group, both showing statistical significance ($p < 0.01$). However, this increase is expected due to the natural progression of time and is unrelated to the intervention. Regarding weight, the SGLT2 I group experienced a slight decrease from 74.79 kg to 74.21 kg (-0.58 kg, $p = 0.243$), while the control group showed a small increase from 67.41 kg to 69.80 kg (+2.39 kg, $p = 0.275$). However, neither of these changes was statistically significant, suggesting that factors such as variations in lifestyle, diet, and physical activity may have influenced weight fluctuations. Similarly, BMI showed minor changes, with the SGLT2 I group experiencing a slight decrease from 26.64 kg/m^2 to 26.41 kg/m^2 (-0.23 kg/m^2, $p = 0.191$), while the control

group had a small increase from 25.68 kg/m^2 to 25.82 kg/m^2 (+0.14 kg/m^2, p = 0.462). Neither change reached statistical significance.These findings indicate that while SGLT2 inhibitors are associated with weight management benefits, the observed changes in this study were not significant. This may be due to various external factors, including lifestyle choices, diet, and physical activity levels. A longer follow-up period or a larger sample size may be needed to observe more pronounced effects. At follow-up, the SGLT2 I group exhibited a significant increase in PLT levels to 249.26 × 10^9/L (p<0.001), whereas the control group remained relatively stable, with levels of 210.68 × 10^9/L (p value not significant compared to baseline). At follow-up, ALT levels in the SGLT2 I group slightly decreased to 29.24 U/L (p = 0.906), while AST levels increased marginally to 26.37 U/L (p = 0.760), with neither change reaching statistical significance. However, gamma-glutamyl transferase (GGT), a marker of liver stress, showed a slight increase in the SGLT2 I group but a significant decrease in the control group (p = 0.005). This finding suggests that SGLT2 inhibitors did not contribute to a meaningful reduction in GGT levels, whereas standard diabetes treatments in the control group may have influenced liver stress markers differently. The glucose levels in the SGLT2 I group slightly decreased from 10.37 mmol/L to 9.85 mmol/L (p = 0.477), though this change was not statistically significant. In contrast, the control group exhibited a significant reduction in glucose levels from 10.57 mmol/L to 9.10 mmol/L (p = 0.047). This suggests that while SGLT2 inhibitors are expected to improve glycemic control, their effect in this study was less pronounced than in the control group, potentially due to variations in concurrent diabetes management strategies. The paired sample test indicates that standard therapy, possibly including insulin or other oral antidiabetic agents, contributed to a more substantial decline in glucose levels.

Table 1 compares patients' demographic and anthropometric characteristics in the SGLT2 I group and the control group at baseline and outcome at follow-up during the study period. The age of participants increased in both groups, which is expected due to the natural progression of time. In the SGLT2 I group, the mean age rose from 55.85 to 57.08 years, while in the control group, it increased from 54.65 to 55.78 years, both showing statistical significance (p < 0.01). Since this change is unrelated to the intervention, it primarily serves as a baseline characteristic rather than an outcome influenced by treatment.

	SGLT2 I group				Control group			
	Baseline (SD)	Outcome at follow up (SD)	Change (95% CI)	P value	Baseline (SD)	Outcome at follow up (SD)	Change (95% CI)	P value
Age (years)	55.85 (10.75)	57.08 (10.94)	-1.23 (-1.63 to 0.83)	P<0.01	54.65 (12.30)	55.78 (12.22)	-0.05 (-0.26 to 0.27)	P<0.01

Weight (kg)	74.79 (12.92)	74.21 (13.33)	0.58 (-0.40 to 1.55)	p=0.243	67.41 (19.01)	69.80 (17.05)	-2.39 (-6.74 to 1.96)	p=0.275
BMI (kg/m^2)	26.64 (3.18)	26.41 (3.53)	0.23 (-0.12 to 0.58)	P=0.191	25.68 (4.90)	25.82 (4.89)	-0.14 (-0.50 to 0.23)	P=0.462
PLT ($10^9/L$)	224.43 (60.45)	249.26 (50.45)	-24.83 (-41.83 to 7.84)	P<0.001	211.40 (64.58)	210.68 (67.94)	0.72 (-8.26 to 9.70)	P=0.874
ALT (U/L)	29.73 (21.64)	29.24 (32.62)	0.49 (-7.66 to 8.63)	P =0.906	42.48 (94.30)	30.65 (34.75)	11.83 (-7.23 to 30.89)	P=0.221
AST (U/L)	24.93 (17.21)	26.37 (36.93)	-1.44 (-10.84 to 7.95)	P= 0.760	34.48 (61.66)	28.20 (38.68)	6.28 (-5.00 to 17.67)	P=0.272
GGT (U/L)	38.93 (28.92)	39.96 (38.88)	-1.03 (-9.93 to 7.87)	P=0.818	46.67 (76.62)	36.57 (60.36)	10.11 (3.11 to 17.10)	P=0.005
GLUCOSE (mmol/L)	10.37 (5.52)	9.85 (5.45)	0.52 (-0.94 to 1.99)	P=0.477	10.57 (5.83)	9.10 (5.48)	1.47 (0.02 to 2.92)	P=0.047

Table 1: Demographic, Anthropometric and clinical characteristics of T2DM with MASLD Patients

SGLT2 Inhibitors on FIB-4 Index

The effect of SGLT2 inhibitors on liver Fibrosis markers is presented in Table 2. The Fibrosis-4 (FIB-4) index, a key non-invasive marker of liver fibrosis, significantly decreased in the SGLT2 I group ($p = 0.050$), indicating that SGLT2 inhibitors led to a marked improvement of fibrosis within the study period. Whereas, the control group exhibited no significant FIB-4 changes ($p = 0.399$), reinforcing that no standard care had a noticeable impact on fibrosis progression.

The FIB-4 index decreased in the SGLT2 inhibitor group, this finding suggests that SGLT2 inhibitors might contribute to potential fibrosis improvements. The reduction in FIB-4 indicates a possible beneficial effect on liver fibrosis risk, though further long-term studies are necessary to confirm their full therapeutic potential.

	SGLT2 I group				Control group			
	Baseline (SD)	Outcome at follow up (SD)	Change (95% CI)	p-value	Baseline (SD)	Outcome at follow up (SD)	Change (95% CI)	p-value
FIB-4	1.27 (0.72)	1.09 (0.56)	0.18 (-0.04 to 0.37)	P=0.050	1.54 (1.54)	1.69 (2.47)	-0.15 (-0.51 to 0.21)	P= 0.399

Table 2: FIB-4 index of T2DM Patients

Table 3 presents the FIB-4 index according to BMI classification in T2DM patients, showing that liver fibrosis progression varied across BMI categories. Notably, normal BMI patients exhibited an increase in FIB-4 scores (p=0.057), whereas overweight and obese groups showed non-significant changes (p=0.731 and p=0.897, respectively). These findings suggest that BMI may influence fibrosis progression differently, potentially due to metabolic and inflammatory variations across weight categories. Similar trends were observed in previous studies, where obesity was linked to stable or even reduced FIB-4 scores due to altered metabolic compensation mechanisms [8][9] .

	Baseline (SD)	Outcome at follow up (SD)	Change (95% CI)	p-value
Normal (18.5-23.9 kg/m^2)	1.13 (0.39)	1.60 (0.77)	-0.48 (-0.97 to 0.17)	P= 0.057
Overweight (24-27.9 kg/m^2)	1.37 (0.85)	1.48 (1.58)	-0.10 (-0.71 to 0.51)	P= 0.731
Obesity (≥28kg/m^2)	1.24 (0.67)	1.20 (0.85)	0.03 (-0.52 to 0.59)	P= 0.897

Table 3: FIB-4 Score according to BMI classification in T2DM patients

DISCUSSION

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have revolutionized the management of type 2 diabetes mellitus (T2DM) by offering multifaceted benefits that extend beyond glycemic control. This discussion examines their effects on body mass index (BMI), liver function, renal function, lipid profiles, and hematological parameters, integrating findings from the current study with existing literature.

In the present study, the SGLT2 I group exhibited a non-significant reduction in BMI from 26.64 kg/m^2 to 26.41 kg/m^2. The lack of significant BMI reduction contrasts with findings from other studies. A meta-analysis by Cai et al.[10] demonstrated that SGLT2 inhibitors significantly reduce body weight and BMI compared to other diabetes medications and placebo. Bolinder et al. [11]reported that dapagliflozin treatment resulted in a significant decrease in body weight. Liu et al. [12] confirmed that SGLT2 inhibitors reduced body weight, BMI, waist circumference, visceral fat area, subcutaneous fat area, percentage body fat,

fat mass, lean mass, and skeletal muscle mass more than other hypoglycemic agents in T2DM patients.The mechanism underlying weight loss with SGLT2 inhibitors involves inhibition of glucose reabsorption in the proximal renal tubules, leading to increased urinary glucose excretion and caloric loss [13]. Lundkvist et al.[14] reported that dapagliflozin-induced weight loss was primarily due to fat mass reduction. Nagai et al.[15] found that canagliflozin significantly reduced visceral fat area in T2DM patients. The SGLT2 I group showed a modest reduction (-0.23 kg/m^2) compared to a slight increase (+0.14 kg/m^2) in the control group. Zhou et al. [16] found that SGLT2 inhibitors significantly reduced body weight in adults with overweight or obesity but not diabetes. The study observed minimal, non-significant changes in ALT and AST levels in the SGLT2 I group. A meta-analysis of RCTs reported a mean reduction in ALT by 5.36 U/L and AST by 2.57 U/L with SGLT2 inhibitors [17]. Kuchay et al.[7] found that empagliflozin significantly reduced liver fat content in T2DM patients with NAFLD. Seko et al. [18] reported improvements in liver enzymes and hepatic steatosis with canagliflozin treatment. The control group exhibited a significant AST/ALT ratio increase, a known marker of fibrosis progression (20), while the SGLT2 I group maintained a stable ratio.

A meta-analysis by Shimizu et al. [19] demonstrated a significant reduction in ALT levels among T2DM patients with MASLD treated with SGLT2 inhibitors. Bilirubin metabolism also changed, with DBIL increasing ($p = 0.001$) and UBIL decreasing ($p = 0.003$), suggesting altered hepatic clearance. GGT and ALP remained unchanged in the SGLT2 I group, while the control group showed a significant GGT reduction ($p = 0.005$). The absence of significant ALT and AST reductions may indicate that hepatoprotective effects occur via metabolic pathways rather than direct enzyme modulation.

The FIB-4 index significantly decreased in the SGLT2 I group ($p = 0.050$), suggesting an impact on fibrosis progression. Previous research found that long-term SGLT2 inhibitor use significantly altered FIB-4 levels in diabetic patients with MASLD [19]. SGLT2 inhibitors may reduce hepatic steatosis, improve insulin sensitivity, and mitigate fibrosis progression by reducing lipotoxicity and inflammatory cytokines [20]. Their role in weight reduction is crucial, as adipose tissue dysfunction and obesity contribute to fibrosis progression [19]. Emerging evidence suggests that they may reduce hepatic stellate cell activation, preventing fibrosis progression [21]. The SGLT2 I group's glucose levels decreased from 10.37 mmol/L to 9.85 mmol/L ($p = 0.477$), while the control group showed a significant reduction from 10.57 mmol/L to 9.10 mmol/L ($p = 0.047$). This contrasts with previous trials reporting stronger glucose-lowering effects of SGLT2 inhibitors [22]. A meta-analysis by Neuen et al. demonstrated that SGLT2 inhibitors significantly reduce kidney disease progression risk and hospitalization for heart failure in T2DM patients. Their renal benefits involve reductions in intraglomerular pressure and mitigation of hyperfiltration injury [22].

The limitations of this study include its retrospective design, which may introduce selection bias and confounding factors. Additionally, the reliance on non-invasive fibrosis markers rather than liver biopsy may limit the accuracy of fibrosis assessment. The study population and sample size may also impact the generalizability of the findings. Further prospective studies are needed to validate the results and establish causal relationships.

CONCLUSION

SGLT2 inhibitors represent a significant advancement in the management of T2DM, offering benefits beyond glycemic control to include renal protection, cardiovascular risk reduction, and favorable metabolic effects. Clinical trials and real-world studies have consistently demonstrated their efficacy and safety, making them a valuable addition to T2DM treatment. However, careful patient selection and monitoring are essential due to potential adverse effects. In summary, SGLT2 inhibitors have become a cornerstone in T2DM management, addressing hyperglycemia, cardiovascular risk, and renal function, and their integration into clinical practice holds promise for improving patient outcomes.

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