



Effects of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes and nonalcoholic fatty liver disease: A cohort study

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Abstract

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) are a novel group of oral medications used to treat type 2 diabetes mellitus (T2DM). Nonalcoholic fatty liver disease (NAFLD), a complication of T2DM, is now recognized as one of the most frequent causes of chronic liver disorders. We aimed to investigate the effects of SGLT2is on hepatic function and glucose homeostasis in patients with T2DM and comorbid NAFLD. To our knowledge, this is the first study in the Arab region to compare the effects of SGLT2is and other antidiabetic medications and to evaluate the outcomes after a 6-month follow-up period in this patient cohort. This cohort study involved 100 patients with T2DM. The patients were divided equally into two groups. The exposed group comprised 50 patients receiving any of the SGLT2is (empagliflozin or dapagliflozin); the non-exposed group comprised 50 patients taking any other oral antidiabetic medication (other than glucagon-like peptide-1 receptor agonists or SGLT2is). The outcomes investigated were glycemic control, hepatic function, and liver fibrosis parameters, investigated at baseline and after 6 months. Significant improvements in glycemic control, hepatic function, and fibrosis parameters were observed in the SGLT2i group after 6 months, as evidenced by laboratory and clinical data ($p < 0.001$). Significant improvements were observed in hemoglobin A1c, Fibrosis-4 index, gamma-glutamyl transferase level, alanine aminotransferase level, and NAFLD fibrosis score ($p < 0.05$). The findings indicate that 6 months of SGLT2i therapy improved fibrosis and glucose homeostasis in patients with T2DM and NAFLD. Therefore, SGLT2is are effective therapeutic agents in this patient population.

Keywords Diabetes mellitus · Sodium-glucose transporter 2 inhibitors · Glucagon-like peptide-1 receptor agonists · Nonalcoholic fatty liver disease · Glycemic control

Abbreviations

SGLT2is	Sodium-glucose cotransporter 2 inhibitors
T2DM	Type 2 diabetes mellitus
NAFLG	Nonalcoholic fatty liver disease
DM	Diabetes mellitus
NASH	Nonalcoholic steatohepatitis
SD	Standard deviation
FBG	Fasting blood glucose
HbA1c	Hemoglobin A1c
HOMA-IR	Homeostatic model assessment for insulin resistance
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGT	Gamma-glutamyl transferase
Fib-4	Fibrosis-4
NAFLD	Nonalcoholic fatty liver disorder
HOMA-IR	Homeostatic model assessment for insulin resistance

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VAT	Visceral adipose tissue
SAT	Subcutaneous adipose tissue
BMI	Body mass index

1 Introduction

Diabetes mellitus (DM) is among the top ten causes of death worldwide. The incidence and prevalence of diabetes are increasing globally. In Egypt, DM is a significant and rapidly growing challenge. United Nation's estimates predict that Egypt's population will reach 102,334,404 by 2025. The International Diabetes Federation reported that the prevalence of diabetes among adults in Egypt was 15.2%, but this may be an underestimation of the actual prevalence (Abouzid et al. 2022).

Nonalcoholic fatty liver disease (NAFLD) is a predominant liver disorder worldwide, impacting approximately 25–30% of the world's population. Globally, nearly 55% of individuals diagnosed with type 2 DM (T2DM) have NAFLD. NAFLD undergoes multiple stages of advancement, with approximately 20–30% of individuals eventually developing nonalcoholic steatohepatitis (NASH) (Yabiku 2021). Patients diagnosed with NASH and concomitant T2DM are more likely to develop hepatocellular carcinoma and cirrhosis (Vargas et al. 2024).

Insulin resistance, dysregulation of lipid metabolism with dysfunctional adipose tissues, excessively high insulin levels, lipotoxicity, oxidative stress, inflammation, and glucotoxicity are crucial factors in the development of NAFLD and NASH (Parthasarathy et al. 2020).

Treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2is) is an emerging strategy for managing T2DM. SGLT2is can exert positive effects on the cardiovascular system and show promise in the management of T2DM (Bica et al. 2023). SGLT2is inhibit glucose reabsorption in the proximal tubule and enhance its excretion via urine. Consequently, SGLT2is lower glucose levels, thereby mitigating lipotoxicity and glucotoxicity (Makri et al. 2021). SGLT2i treatment offers potential benefits in enhancing insulin sensitivity by improving caloric disposition, weight loss, and mitigating glucose toxicity. Moreover, SGLT2is contribute to lowering inflammation, reducing oxidative stress, boosting the activity of beta cells, and stimulating the secretion of alpha cells. Additionally, reports suggest that these substances exhibit pleiotropic effects on various complications and exert regulatory effects on macrovascular events. Furthermore, they have been shown exert positive effects on hepatic dysfunction, fibrosis, and steatosis in both animal models and human trials. Consequently, SGLT2is are anticipated to be effective in treating individuals with T2DM and comorbid NASH or NAFLD (Ito et al. 2017; Takahashi et al. 2022).

To this end, this study aimed to examine the impact of SGLT2i use on the hepatic function, glycemic control, and liver fibrosis parameters of patients with T2DM and NAFLD. To our knowledge, this study is the first in the Arab region to compare the effects of SGLT2i in patients with T2DM and NAFLD to those of other antidiabetic medications, and to evaluate the outcomes after a 6-month follow-up period.

2 Methods

This was a cohort study conducted at a tertiary care facility between February and November 2023. The study was reviewed and approved by the Institute's Ethical Committee at the Faculty of Medicine, Alexandria University (Approval No. 0306713). Prior to participation, all eligible individuals were provided with detailed information about the study's objectives, design, procedures, and their rights as participants. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

The study involved 100 individuals with T2DM, recruited from the Internal Medicine Department of the participating hospital. The exposure investigated in this study was the use of SGLT2i medications. The SGLT2i group (exposed group) comprised 50 individuals who had initiated SGLT2i therapy (empagliflozin or dapagliflozin) within the previous 2 weeks, whereas the non-SGLT2i group (non-exposed group) comprised 50 individuals receiving other oral anti-diabetic medications, excluding glucagon-like peptide-1 receptor agonists (GLP-1RAs) or SGLT2is.

2.1 Sample selection

Convenience sampling was employed to recruit participants who received follow-up care at the hospital and met the inclusion–exclusion criteria, until the required sample size was reached.

The inclusion criteria were as follows: adults aged > 18 years, of either sex, diagnosed with T2DM and presenting with signs and symptoms of NAFLD.

The exclusion criteria were as follows: individuals receiving GLP-1RA or insulin treatment; those with severe diabetes-associated complications, such as severe diabetic retinopathy, nephropathy, or neuropathy; and those diagnosed with type 1 DM or a history of significant cardiovascular disorders, Wilson disorder, autoimmune liver disorder, drug-induced hepatotoxicity, viral hepatitis, or hemochromatosis. Individuals with missing information on exposure, outcome, or key covariates were excluded from the analysis.

2.2 Follow-up

Patients were followed up for 6 months after enrollment in the study. Laboratory and clinical data were compared between the two groups at baseline and after 6 months. Only patients who had complete follow-up were included in the analysis.

2.3 Outcome measures

The outcomes investigated were glycemic control, hepatic function, and liver fibrosis parameters. Glycemic control was defined according to the American Diabetes Association (ADA) recommendations for most non-pregnant adults with type 2 diabetes mellitus (T2DM), using the following criteria: fasting blood glucose (FBG) ≤ 130 mg/dL and glycated hemoglobin (HbA1c) $\leq 7.0\%$. A complete history of all patients was gathered, and a thorough general examination, including body mass index (BMI), was performed. Venous blood samples were collected after overnight fasting and were used to determine fasting blood glucose (FBG), hemoglobin A1c (HbA1c), fasting serum insulin, and ferritin concentrations. Liver function was assessed by measuring alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) levels using standard laboratory techniques. Insulin resistance was estimated by determining homeostatic model assessment for insulin resistance (HOMA-IR) using the following formula: (fasting insulin [IU/mL] $\times$ FBG [mg/dL])/405 (Haffner et al. 1996). Subcutaneous adipose tissue (SAT, cm²) and visceral adipose tissue (VAT, cm²) were measured at the umbilical level using computed tomography images and the Fat Scan program (N2 System Co., Osaka, Japan) (Yoshizumi et al. 1999).

The Fibrosis-4 (Fib-4) index (mean $\pm$ standard deviation [SD]) was calculated at the time of the first FibroScan and repeated after 6 months of management using the following formula: Fib-4 index = (AST [IU/L] $\times$ Age [y]) / (platelet count [10^9 /L] $\times \sqrt{\text{ALT [IU/L]}}$). A Fib-4 score < 1.3 had a sensitivity of 82% for the absence of advanced fibrosis. In contrast, a Fib-4 score > 2.67 would have a 93% specificity for advanced fibrosis (MDCalc 2024; Alkhouri and McCullough 2012).

The NAFLD fibrosis score was estimated using the following formula: $-1.675 + 0.037 \times \text{age (y)} + 0.094 \times \text{BMI (kilograms per square meter)} + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet count (} \times 10^9/\text{L)} - 0.66 \times \text{albumin (g/dL)}$ (MDCalc 2024). An NAFLD fibrosis score < -1.455 had a sensitivity of 89% for the absence of advanced fibrosis. In contrast, an NAFLD fibrosis score > 0.676 had 89% specificity for advanced fibrosis.

Each FibroScan was performed with individuals lying down with their right arm fully extended and held in place for 10 s while holding their breath. Following the manufacturer's guidance, all patients underwent an initial scan using the M probe (3.5 Megahertz) on the right hepatic lobe region of the abdomen, followed by a subsequent scan using the XL probe (2.5 Megahertz). To determine liver stiffness measurement (LSM), at least 10 readings were obtained, and the median and interquartile range (IQR), both expressed in kilopascals (kPa), were calculated. Liver stiffness levels of 5.5 kPa were considered normal. Values less than 8 kPa indicated a low risk of advanced fibrosis, while those between 8 and 12 kPa indicated a high risk of advanced fibrosis. Simultaneous liver steatosis measurements were obtained using controlled attenuation parameter (CAP) values in dB/m, which were colocalized with valid LSMs (Eddowes et al. 2019).

2.4 Sample size

The sample size was calculated using OpenEpi, version 3, open-source calculator (SSCohort), based on the findings of Takahashi et al., who reported that NAFLD resolved in 66.7% and 27.3% of cases in the SGLT2i and comparison groups, respectively (Takahashi et al. 2022). With a 95% confidence level and 5% margin of error, the calculated sample size was 84 participants. An additional 15% were enrolled to account for the risk of loss to follow-up.

2.5 Statistical analysis

IBM SPSS for Windows version 24 (IBM Corp., Armonk, N.Y., USA) was used for data entry, data processing, and statistical analysis. Regarding descriptive statistics, quantitative data are presented as mean and SD (mean $\pm$ SD), whereas qualitative data are presented as numbers and percentages. With respect to analytical statistics, group comparisons, especially those regarding qualitative information, were conducted using the chi-square test (χ^2). An independent samples *t*-test was used to compare the means of quantitative data between two independent groups with normal distribution, while a paired *t*-test was used to compare the means within the same group at two different time points. Statistical significance was set at $p < 0.05$.

3 Results

One hundred participants met the eligibility criteria and agreed to participate. The patients were divided into two equal groups based on the use of SGLT2is. The number of patients excluded from the study were not quantified. These patients could not be tracked because of incomplete records or

inadequate documentation. Details on the types and doses of SGLT2 inhibitors, along with the distribution of non-SGLT2i medications, are provided in Supplementary Table 1. No significant differences were observed between the groups in terms of age, sex, BMI, VAT, and SAT at baseline (Table 1). Prior to statistical comparisons, normality testing was conducted and the data were found to be normally distributed.

At baseline, no significant differences were observed between the groups in terms of FBG, HbA1c, fasting serum insulin, HOMA-IR, AST, ALT, GGT, and ferritin levels ($p > 0.05$). In addition, no significant differences were observed in the Fib-4 index, NAFLD fibrosis scores, and FibroScan readings ($p = 0.48, 0.06$, and 0.23 , respectively) between the groups (Table 2).

Table 1 Distribution of demographic data and weight parameters between the groups at baseline

Variable		SGLT2i Group (n = 50)	Non-SGLT2i Group (n = 50)	<i>p</i> value
Age	Mean $\pm$ SD	47.5 $\pm$ 7.21	46.3 $\pm$ 7.01	0.4
Sex	Male n (%)	22 (44%)	24 (48%)	0.68
	Female n (%)	28 (56%)	26 (52%)	
BMI	Mean $\pm$ SD	27.3 $\pm$ 5.4	27.9 $\pm$ 4.6	0.55
VAT (cm ²)	Mean $\pm$ SD	127.9 $\pm$ 41.9	124.9 $\pm$ 31.1	0.68
SAT (cm ²)	Mean $\pm$ SD	225.4 $\pm$ 90.0	248.5 $\pm$ 82.3	0.18

Statistical significance was assessed using the independent samples *t*-test. *p* values < 0.05 are statistically significant. SD, standard deviation; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index; SGLT2i, sodium-glucose cotransporter 2 inhibitor

After 6 months of follow-up, significant differences were observed in the BMI, VAT, and SAT between the SGLT2i and non-SGLT2i groups (Table 3; $p = 0.01, 0.01$, and 0.02 , respectively). Additionally, significant differences were observed in the FBG, HbA1c, fasting serum insulin, HOMA-IR, AST, ALT, GGT, and ferritin levels between the groups ($p < 0.001$). Significant differences were also observed in the Fib-4 index, NAFLD fibrosis score, and FibroScan readings ($p < 0.001$).

When comparing the results of the SGLT2i group at baseline and after 6 months, significant improvements were observed in glycemic control, hepatic function, and fibrosis parameters, as evidenced by the laboratory and clinical data ($p < 0.001$) (Table 4). The differences in the NAFLD fibrosis score, Fib-4 index, and FibroScan readings at baseline and after 6 months in the SGLT2i group are shown in Fig. 1.

In contrast, comparisons within the non-SGLT2i group showed significant improvements in glycemic control, while no significant improvements in hepatic function and fibrosis parameters were observed, as evidenced by the laboratory and clinical data (Table 5). The differences between the NAFLD fibrosis score, Fib-4 index, and FibroScan readings at baseline and after 6 months in the non-SGLT2i group are shown in Fig. 2.

4 Discussion

The incidence of NAFLD is increasing simultaneously with the increasing prevalence of obesity. NAFLD has emerged as the leading cause of chronic liver disease, which affects

Table 2 Distribution of laboratory and clinical data between the groups at baseline

Variable	SGLT2i Group (Mean $\pm$ SD)	Non-SGLT2i Group (Mean $\pm$ SD)	<i>p</i> value
FBG (mg/dL)	137.8 $\pm$ 53	135.3 $\pm$ 40.3	0.79
HbA1c (%)	8.46 $\pm$ 1.52	7.9 $\pm$ 1.36	0.05
Fasting serum insulin (μ U/mL)	12.1 $\pm$ 2.45	11.45 $\pm$ 3.1	0.24
HOMA-IR	3.56 $\pm$ 2.51	3.89 $\pm$ 2.1	0.47
AST (U/L)	35.8 $\pm$ 12.8	39.15 $\pm$ 7.3	0.11
ALT (U/L)	55.9 $\pm$ 9.8	58.7 $\pm$ 5.5	0.08
GGT (U/L)	69.5 $\pm$ 15.07	71.15 $\pm$ 10.5	0.52
Ferritin (ng/mL)	91.2 $\pm$ 29.4	93.9 $\pm$ 31.95	0.66
Fib-4 index	1.82 $\pm$ 0.34	1.95 $\pm$ 0.62	0.48
Nonalcoholic fatty liver disorder fibrosis score	-0.84 $\pm$ 0.53	-0.79 $\pm$ 0.61	0.06
FibroScan	8.2 $\pm$ 1.1	7.9 $\pm$ 1.9	0.23

Statistical significance was assessed using the independent samples *t*-test. *p* values < 0.05 are statistically significant. SD, standard deviation; SGLT2i, sodium-glucose cotransporter 2 inhibitor; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; Fib-4, Fibrosis-4

Table 3 Distribution of follow-up laboratory and clinical data after 6 months between the groups

Variable	SGLT2i Group (Mean $\pm$ SD)	Non-SGLT2i Group (Mean $\pm$ SD)	<i>p</i> value
BMI	25.3 $\pm$ 5.4	27.5 $\pm$ 4.4	0.01
VAT (cm ²)	101.9 $\pm$ 38.7	119.9 $\pm$ 30.2	0.01
SAT (cm ²)	197.4 $\pm$ 73.9	235.5 $\pm$ 64.7	0.02
FBG (mg/dL)	119.3 $\pm$ 34.1	129.5 $\pm$ 46.7	0.001
HbA1c (%)	6.34 $\pm$ 1.21	7.21 $\pm$ 1.13	<0.001
Fasting serum insulin (μ U/mL)	10.25 $\pm$ 3.07	11.55 $\pm$ 3.31	<0.001
HOMA-IR	3.17 $\pm$ 0.84	3.67 $\pm$ 0.9	<0.001
AST (U/L)	24.55 $\pm$ 3.63	39.7 $\pm$ 9.8	<0.001
ALT (U/L)	29.4 $\pm$ 6.55	37.15 $\pm$ 6.07	<0.001
GGT (U/L)	41 $\pm$ 10.25	66.15 $\pm$ 6.92	0.006
Ferritin (ng/mL)	51.8 $\pm$ 18.6	92.3 $\pm$ 12.7	<0.001
Fib-4 index	1.55 $\pm$ 0.35	2.39 $\pm$ 0.18	0.04
Nonalcoholic fatty liver disorder fibrosis score	-1.29 $\pm$ 0.15	-0.54 $\pm$ 0.07	<0.001
FibroScan	5.2 $\pm$ 3.1	8.6 $\pm$ 2.3	<0.001

Statistical significance was assessed using the independent samples *t*-test. *p* values <0.05 are statistically significant. SD, standard deviation; SGLT2i, sodium-glucose cotransporter 2 inhibitor; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; Fib-4, Fibrosis-4; BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue

Table 4 Distribution of follow-up laboratory and clinical data in the SGLT2i group at baseline and after 6 months

Variable	SGLT2i Group at Baseline (Mean $\pm$ SD)	SGLT2i Group after 6 Months (Mean $\pm$ SD)	<i>p</i> value
FBG (mg/dL)	137.8 $\pm$ 53	119.3 $\pm$ 34.1	0.04
HbA1c (%)	8.46 $\pm$ 1.52	6.34 $\pm$ 1.21	<0.001
Fasting serum insulin (μ U/mL)	12.1 $\pm$ 2.45	10.25 $\pm$ 3.07	0.001
HOMA-IR	3.56 $\pm$ 2.51	3.17 $\pm$ 0.84	<0.001
AST (U/L)	35.8 $\pm$ 12.8	24.55 $\pm$ 3.63	<0.001
ALT (U/L)	55.9 $\pm$ 9.8	29.4 $\pm$ 6.55	<0.001
GGT (U/L)	69.5 $\pm$ 15.07	41 $\pm$ 10.25	<0.001
Ferritin (ng/mL)	91.2 $\pm$ 29.4	51.8 $\pm$ 18.6	<0.001
Fib-4 index	1.82 $\pm$ 0.34	1.55 $\pm$ 0.35	<0.001
NAFLD fibrosis score	-0.84 $\pm$ 0.53	-1.29 $\pm$ 0.15	<0.001
FibroScan	8.2 $\pm$ 1.1	5.2 $\pm$ 3.1	<0.001

Statistical significance was assessed using the paired *t*-test. *p* values <0.05 are statistically significant. SD, standard deviation; SGLT2i, sodium-glucose cotransporter 2 inhibitor; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; Fib-4, Fibrosis-4; NAFLD, nonalcoholic fatty liver disorder

approximately 25% of the global population (Brunt 2005). SGLT2is can help mitigate many risk factors associated with arteriosclerosis, including diabetes, obesity, hypertension, and dyslipidemia. Consequently, this treatment option has recently garnered significant interest, especially among clinicians interested in the management of NAFLD (Angulo et al. 2007).

The present study indicated that a 6-month treatment with SGLT2is in individuals with diabetes and NAFLD improved glycemic control, body weight/composition parameters (used as indicators of obesity), HOMA-IR index scores, and hepatic function, including liver fibrosis.

This study showed a trend toward weight loss, and the difference was significant, as evidenced by the lower levels of VAT and SAT and lower BMI values in the SGLT2i group. A systematic review by Ong Lopez and Pajimna (2024) reported that SGLT2is resulted in a significant decrease in subcutaneous fat area and visceral fat mass (Ong Lopez and Pajimna 2024).

Improvements in BMI and glycemic control achieved with SGLT2is may contribute to improving liver steatosis. Nevertheless, compelling evidence indicates that SGLT2is have a positive impact on hepatic fibrosis in rodents and steatosis in both humans and rodents. Importantly, these effects are not solely attributed to a reduction in body mass, suggesting an independent mechanism through which SGLT2is improve hepatic conditions correlated with NAFLD, regardless of their influence on obesity (Shimizu et al. 2019).

Fig. 1 Distribution of data for the nonalcoholic fatty liver disease fibrosis score, Fib-4 index, and FibroScan readings in the SGLT2i group at baseline and after 6 months. SGLT2i, sodium–glucose cotransporter 2 inhibitor; Fib-4, Fibrosis-4; NAFLD, nonalcoholic fatty liver disease

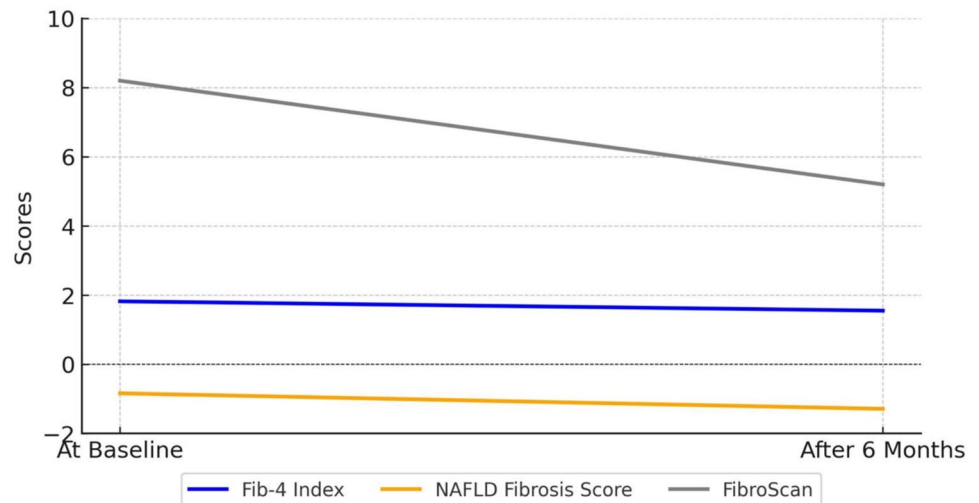
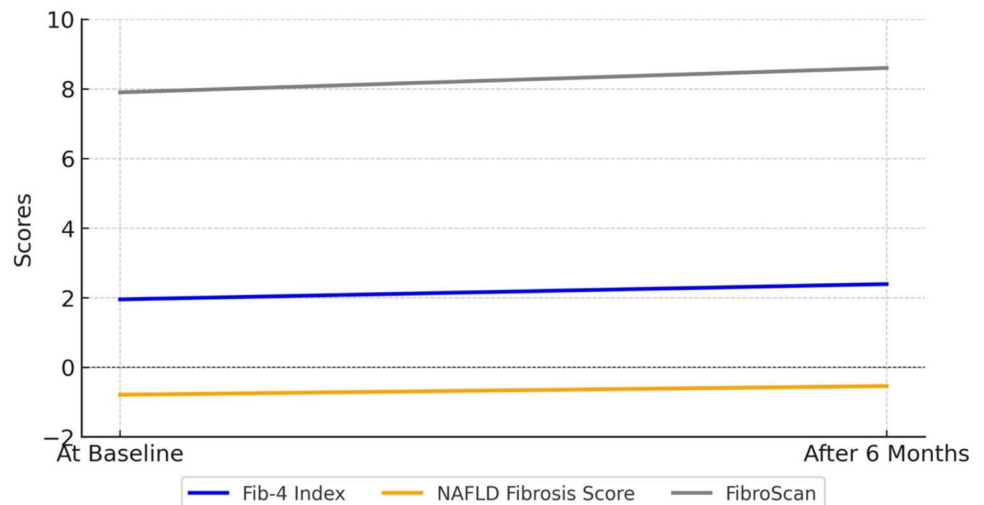


Table 5 Distribution of laboratory and clinical data in the non-SGLT2i group at baseline and after 6 months

Variable	Non-SGLT2i Group at Baseline (Mean ± SD)	Non-SGLT2i Group after 6 Months (Mean ± SD)	<i>p</i> value
FBG (mg/dL)	135.3 ± 40.3	129.5 ± 46.7	<0.001
HbA1c (%)	7.9 ± 1.36	7.21 ± 1.13	0.006
Fasting serum insulin (μU/mL)	11.45 ± 3.1	11.55 ± 3.31	0.004
HOMA-IR	3.89 ± 2.1	3.67 ± 0.9	<0.001
AST (U/L)	39.15 ± 7.3	39.7 ± 9.8	0.73
ALT (U/L)	58.7 ± 5.5	37.15 ± 6.07	0.50
GGT (U/L)	71.15 ± 10.5	66.15 ± 6.92	0.87
Ferritin (ng/mL)	93.9 ± 31.95	92.3 ± 12.7	0.74
Fib-4 index	1.95 ± 0.62	2.39 ± 0.18	-
NAFLD fibrosis score	-0.79 ± 0.61	-0.54 ± 0.07	0.49
FibroScan	7.9 ± 1.9	8.6 ± 2.3	0.10

Statistical significance was assessed using the paired t-test. *p* values <0.05 are statistically significant. SD, standard deviation; SGLT2i, sodium–glucose cotransporter 2 inhibitor; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; Fib-4, Fibrosis-4; NAFLD, nonalcoholic fatty liver disorder

Fig. 2 Distribution of data for the nonalcoholic fatty liver disease fibrosis score, Fib-4 index, and FibroScan readings in the non-SGLT2i group at baseline and after 6 months. SGLT2i, sodium–glucose cotransporter 2 inhibitor; Fib-4, Fibrosis-4; NAFLD, nonalcoholic fatty liver disease



The findings of this study contrast with those of Phrueksotsai et al. (Phrueksotsai et al. 2021), who investigated the impact of dapagliflozin use on the levels of hepatic and visceral fat, as well as associated biochemical markers, in patients with T2DM and NAFLD. Of the 40 participants, 38 completed the trial (18 in the dapagliflozin group and 20 in the placebo group). The researchers found no significant differences in the visceral-to-subcutaneous fat ratio (V/S ratio) across the groups.

The present study found significant differences in FBG, HbA1c, fasting serum insulin, HOMA-IR, AST, ALT, GGT, and ferritin levels between the groups. These findings contrast with the results obtained by Phrueksotsai et al. (Phrueksotsai et al. 2021), who found no significant differences in fasting glucose, HbA1c, HOMA-IR, AST, ALT, and GGT levels between the studied groups. Tofogliflozin has a notable effect on enhancing insulin sensitivity and increasing glucose absorption in peripheral tissues among Japanese individuals diagnosed with T2DM (Le and Loomba 2012).

An improvement in hepatic insulin resistance, as assessed using the HOMA-IR score, was observed. Treatment with SGLT2is improved hyperinsulinemia, perhaps by enhancing hepatic insulin clearance, leading to a reduction in insulin levels. These factors enhance liver function (Yabiku et al. 2020).

Therapy with SGLT2is improves fatty liver conditions in diabetic KK-Ay mice (Suzuki et al. 2014). Improvements were also shown in a rat model of NASH induced by a diet lacking choline (Hayashizaki-Someya et al. 2015). Honda et al. demonstrated that the injection of the SGLT2i, ipragliflozin delays the development of NASH by improving insulin resistance and reducing lipotoxicity in mice (Honda et al. 2016). The EFFECT-II Study, a randomized placebo-controlled trial, showed that the SGLT2i, dapagliflozin positively affected hepatocyte injury biomarkers and plasma concentrations of fibroblast growth factor 21 in patients with NAFLD associated with T2DM. This suggests that dapagliflozin can reduce cellular damage and fibrosis in these patients (Eriksson et al. 2018).

The favorable effects of SGLT2is on fatty liver may be attributed to many factors, including a negative energy balance caused by increased urine glucose excretion, suppression of fat production in the liver, and promotion of fat breakdown (Shibuya et al. 2018).

The present study found significant differences in the NAFLD fibrosis score, Fib-4 index, and FibroScan results between the studied groups. Our findings contrast with those of Shimizu et al. (Shimizu et al. 2019), who found no significant differences in the Fib-4 index and NAFLD fibrosis score between the studied groups.

Laboratory data from 6 months of follow-up revealed significant differences in FBG, HbA1c, fasting serum insulin, and HOMA-IR between the study groups, demonstrating

improved glycemic control. Additionally, our findings showed a significant improvement in hepatic function, as demonstrated by AST, ALT, and GGT levels. Reduced circulating transaminase activity suggests a reduction in ongoing liver damage. These findings are important for understanding the effect of therapies involving SGLT2i and the underlying mechanisms of T2DM. Based on these findings, SGLT2i can reduce both insulin and postprandial glucose levels. The primary effect of SGLT2i therapy is enhanced elimination of insulin by the liver. The HOMA-IR index indicates the presence of insulin resistance in the liver. Improvements in hepatic insulin resistance, assessed using the HOMA-IR score, were also noted. SGLT2i therapy improves hyperinsulinemia, possibly by enhancing hepatic insulin clearance, leading to reduced insulin levels. These factors enhance liver function (Yabiku et al. 2020).

In the present study, a significant decrease in serum ferritin concentrations was observed after using SGLT2is for 6 months. As SGLT2is are not present in hepatocytes, the improvement in hepatocyte function can be attributed to the indirect effects of SGLT2is. Furthermore, patients with NASH often present with an excess of hepatic iron and hyperferritinemia (Nelson et al. 2011). Additionally, iron overload in the livers of mice lacking leptin receptors and being overfed with iron leads to oxidative stress and inflammasome activation, resulting in hepatocyte damage (Handa et al. 2016). This suggests that reducing iron overload could be a potential mechanism through which SGLT2is improve or prevent hepatocyte damage in NAFLD.

Clinical data after 6 months of follow-up showed significant improvements in the NAFLD fibrosis score, Fib-4 index, and FibroScan results in the SGLT2i group. SGLT2is may be an efficacious therapeutic option for individuals diagnosed with T2DM who also have liver fibrosis. SGLT2i-based therapy may be suitable for treating fatty liver because of its ability to reduce glucose levels and resolve ascites in mice fed a high-fat diet. Importantly, it does not have any negative effects on hemodynamics, even in the presence of liver fibrosis (Suzuki et al. 2014). Ong Lopez and Pajimna (2024) reported that patients receiving SGLT2i treatment showed significant decreases in the Fib-4 index at week 48 compared with those in the non-SGLT2i group, which received alternative oral hypoglycemic medicines (Ong Lopez and Pajimna 2024). After administering SGLT2i treatment, a notable disparity in means was detected for the CAP and Fib-4 index ($p=0.005$), compared with that in the non-SGLT2i group.

Additionally, our findings are consistent with those of Chehrehgosha et al. (Hayashizaki-Someya et al. 2015), who reported a significant reduction in liver fibrosis after 20 weeks in the empagliflozin group (LSM: 6.83 ± 2.44 to 6.01 ± 1.65 kPa; $p=0.005$). In contrast, no significant

change in the fibrosis score was observed in the placebo groups (7.49 ± 2.65 to 7.17 ± 2.67 kPa; $p = 0.27$).

These data indicate that SGLT2i-based treatment may reduce hepatic fibrosis and steatosis in both rats and humans, regardless of weight reduction. This implies that SGLT2is may have a mechanism that improves liver conditions associated with NAFLD, irrespective of their impact on obesity (Takahashi et al. 2022).

While the use of non-invasive surrogate markers—such as FibroScan, the Fibrosis-4 (FIB-4) index, and the NAFLD fibrosis score—provided valuable insights into liver fibrosis staging, a key limitation of this study is the absence of histological confirmation via liver biopsy. Although these non-invasive tools are widely accepted in both clinical practice and research, they cannot fully replicate the diagnostic accuracy and staging precision offered by liver biopsy, which remains the gold standard for assessing hepatic fibrosis. This limitation may have resulted in the misclassification of fibrosis severity, particularly in patients with borderline or indeterminate scores. Future research incorporating histopathological evaluation is essential to validate and reinforce our findings.

This study has some limitations. First, we did not assess the histology of the liver before and after the use of each medication; hence, the effect of SGLT2is on liver tissue remains uncertain. Second, because the criteria for selecting participants in this trial did not restrict enrollment to individuals with advanced NASH but included individuals with mild-to-moderate NASH, evaluating the efficacy of SGLT2is requires caution. Nevertheless, including cases with varying degrees of NAFLD severity in this trial allowed us to show that SGLT2is may prevent the progression of NASH, improve NASH, and reduce liver fibrosis. Hence, SGLT2is may have a positive impact on patients across all stages of NAFLD. The inclusion criteria did not specify a certain SGLT2i dose, and patients receiving either dapagliflozin or empagliflozin, regardless of dose, were included in the study. However, by excluding participants with incomplete data, we might have inadvertently introduced selection bias, as those with complete data might systematically differ from those with incomplete data. Although normality testing confirmed that the data were normally distributed, no formal correction for multiple comparisons was applied despite evaluating multiple endpoints. This may increase the risk of Type I error, and thus, the findings should be interpreted with caution. Also, given the observational design and reliance on descriptive and bivariate analyses, the possibility of residual confounding remains—even though no significant baseline differences were observed. While multivariate or propensity score methods were not deemed necessary, their use could have enhanced confounder adjustment and strengthened causal inference. Additionally, the use of convenience sampling may introduce selection bias and limits the generalizability of our findings, as the study population may not fully

represent the broader T2DM and NAFLD patient population in other clinical settings. Future studies should aim to ensure complete documentation and transparent reporting to enhance the reliability and applicability of results.

5 Conclusion

The primary aim of this study was to evaluate the therapeutic effects of SGLT2is and compare them with other oral anti-diabetic agents. The study findings suggest that 6 months of SGLT2i therapy improves glycemic parameters, liver function, and fibrosis in patients with T2DM and NAFLD. Although the study demonstrates potential associations between SGLT2i use and these improvements, the absence of liver biopsy remains a significant limitation. As liver biopsy is considered the gold standard for staging hepatic fibrosis, reliance on surrogate markers may reduce the precision and accuracy of fibrosis assessment. While the results are encouraging, they should be interpreted with caution. A strength of this study lies in its use of multiple validated non-invasive fibrosis scores, which offer a multifaceted assessment of hepatic health. However, randomized controlled trials incorporating biopsy-confirmed endpoints and dose-specific evaluations are warranted to confirm causality and strengthen the evidence base for clinical decision-making.

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Data availability The data associated with this study have not been deposited into a publicly available repository; however, the data will be made available on request.

Declarations

Ethics approval The study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the ethics committee of Alexandria University's faculty of medicine (IRB no. 0306713). Each participant voluntarily participated in the study and provided

informed consent. Participants were free to withdraw from the study at any time, without any effect on their hospital services. Confidentiality and anonymity of the participants was ensured throughout the study.

Competing interests The authors declare that they have no competing financial interests or personal relationships that may have influenced the work reported in this study.

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