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The effect of empagliflozin on non-alcoholic fatty liver disease-related parameters in patients with type 2 diabetes mellitus: a randomized controlled trial

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Abstract

Background and objective The effects of Empagliflozin on liver health in patients with Type 2 Diabetes Mellitus (T2DM) have not been fully elucidated. This study aimed to assess the impact of Empagliflozin on liver steatosis and related biomarkers in T2DM patients.

Methods A before-after clinical trial was conducted with 119 T2DM patients aged 20 to 70 with fatty liver, recruited from Laghman Hakim Hospital, Tehran, Iran. Participants were administered Empagliflozin for 6 months, with clinical and laboratory assessments conducted at baseline, 3 months, and 6 months. Liver function was evaluated through blood tests and imaging, including ultrasound and Magnetic resonance imaging (MRI), to assess hepatic steatosis. Biomarkers such as HbA1c, fasting blood glucose, insulin, lipid profile, and liver enzymes were measured. Insulin resistance was estimated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) formula. Data were analyzed using SPSS 26 and STATA 14.

Results A total of 119 patients (Intervention ($N=69$), Control ($N=50$)) were participated. The intervention group demonstrated a significant reduction in liver fat grade compared to the control group, with 17.5% of patients showing a reduction from grade 3 to grade 1 on MRI and 6% in the control group. The odds of worsening fatty liver in the control group were 48 times higher (95% CI: 15.5, 148.5) on MRI and 52 times higher (95% CI: 15.2, 178.1) on ultrasound, compared to the intervention group (NNT = 2). After 6 months, the intervention group showed significantly lower risks for ALT (RR: 0.72, 95% CI: 0.62–0.84), AST, and alkaline phosphatase (Alkp) abnormalities. Liver enzyme levels (ALT, AST, GGT) and systolic blood pressure (SBP) decreased significantly in the Empagliflozin group, with mean differences of -15.33 (95% CI: -18.8, -11.88) for ALT, -12.82 (95% CI: -15.5, -10.13) for AST, and −6.31 (95% CI: -8.65, -3.97) for systolic blood pressure (SBP).

Conclusion These findings suggest that Empagliflozin could be an effective adjunctive therapy for managing liver dysfunction in T2DM patients with NAFLD.

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Trial registration Registered retrospectively in the Iranian Registry of Clinical Trials (IRCT20210811052150N1) on April 16,2023 Access at https://irct.behdasht.gov.ir/search/result?query=IRCT20210811052150N1.

Keywords Empagliflozin, Type 2 diabetes mellitus, Non-alcoholic fatty liver, Liver dysfunction

Introduction

Non-alcoholic fatty liver disease (NAFLD) represents one of the most common chronic liver conditions worldwide, characterized by the accumulation of fat in the liver in the absence of excessive alcohol consumption [1]. NAFLD encompasses a spectrum of hepatic abnormalities, ranging from simple steatosis (fatty liver) to non-alcoholic steatohepatitis (NASH), which can progress to liver fibrosis, cirrhosis, and even hepatocellular carcinoma [2, 3]. The global prevalence of NAFLD is increasing, and it is closely associated with metabolic disorders such as obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) [4]. Indeed, individuals with T2DM are at an elevated risk for the development and progression of NAFLD, with studies suggesting that more than 50% of people with diabetes may also have fatty liver disease [5].

The pathophysiological relationship between T2DM and NAFLD is multifactorial, with insulin resistance being a central factor in both conditions. Insulin resistance increases free fatty acid levels, which promotes hepatic fat accumulation [6]. Additionally, elevated glucose levels and dyslipidemia further exacerbate liver damage, creating a vicious cycle of worsening hepatic steatosis and insulin resistance [7]. The growing recognition of the bidirectional association between T2DM and NAFLD has underscored the need for effective therapeutic strategies that address both diseases simultaneously [8].

Empagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, is a relatively new class of oral antidiabetic medications that has gained widespread use in the management of T2DM. By inhibiting the SGLT2 transporter in the kidney's proximal tubule, empagliflozin reduces glucose reabsorption, increasing urinary glucose excretion and reducing blood glucose levels [9]. In addition to its glucose-lowering effects, empagliflozin has been shown to have several extraglycemic benefits, including weight loss, blood pressure reduction, and improved cardiovascular outcomes, which have been demonstrated in large clinical trials such as EMPA-REG OUTCOME [10]. Recent studies have suggested that empagliflozin may also have potential benefits for liver health, particularly in patients with NAFLD and NASH, although the underlying mechanisms remain incompletely understood [11, 12].

Several lines of evidence support the hypothesis that SGLT2 inhibitors, including empagliflozin, may have beneficial effects on NAFLD. Preclinical studies have shown that SGLT2 inhibition reduces liver fat accumulation, improves liver function markers, and decreases inflammation in animal models of fatty liver [13]. Furthermore, clinical trials have reported favorable effects of SGLT2 inhibitors on liver enzymes (such as ALT and AST) and markers of hepatic fibrosis in patients with NAFLD. The exact mechanisms by which empagliflozin may influence liver fat metabolism remain a topic of active research, but potential pathways include the modulation of lipid metabolism, improvement of insulin sensitivity, reduction of systemic inflammation, and promotion of weight loss—all of which are central to the pathophysiology of NAFLD [14].

Despite promising preclinical and early clinical data, the impact of empagliflozin, specifically on NAFLD in T2DM patients, requires further exploration. While some studies have demonstrated improvements in liver enzymes and other markers of liver function in individuals treated with SGLT2 inhibitors, other trials have yielded mixed results [15]. The heterogeneity of patient populations, variations in study design, and differences in the stage of liver disease may contribute to these discrepancies. Therefore, it is crucial to critically evaluate the available evidence on the effectiveness of empagliflozin in managing NAFLD in patients with T2DM, focusing on liver-related outcomes such as liver fat content, fibrosis, and inflammation [16].

As the prevalence of both T2DM and NAFLD continues to rise globally, understanding the therapeutic potential of empagliflozin in this dual disease context could offer new opportunities for improving liver health in this high-risk population. Furthermore, elucidating the relationship between SGLT2 inhibitors and NAFLD may contribute to developing novel treatment strategies targeting glucose control and liver pathology, offering a more integrated approach to managing these interconnected metabolic disorders [17]. Therefore, the present study aimed to explore the effect of empagliflozin on NAFLD-related parameters in patients with T2DM.

Materials and methods

This study was conducted as a before-after clinical trial to assess the effect of Empagliflozin on liver health in patients with T2DM, particularly focusing on liver steatosis and related biomarkers. This study received ethical approval from the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ethical code:.....), underscoring the commitment to ethical research practices.

Study population

The study included patients aged 20 to 70 years diagnosed with T2DM who visited Laghman Hakim Hospital for treatment with Empagliflozin in 2021. Patients were selected based on specific inclusion and exclusion criteria, with a total sample size of 70.

Inclusion and exclusion criteria

The study included adults aged 20 to 70 years with a diagnosis of T2DM and fatty liver who were eligible for treatment with Empagliflozin. Participants had no prior history of Empagliflozin use, an estimated glomerular filtration rate (GFR) greater than 35 mL/min/1.73 m^2, and an HbA1c level of 7.5% or less. All participants or their legal guardians provided written informed consent. Also, exclusion criteria included a history of advanced liver or kidney diseases, recent (within the last 3 months) heart surgery or angioplasty, bariatric surgery within the previous 2 years or other gastrointestinal surgeries causing chronic malabsorption, history of bleeding disorders or conditions causing hemolysis (e.g., malaria, babesiosis, hemolytic anemia), history of cancer (except basal cell carcinoma) or cancer treatment in the last 5 years, use of anti-obesity medications (e.g., sibutramine, orlistat) in the previous 3 months or other weight-loss treatments leading to unstable body weight, current use of systemic steroids or other uncontrolled endocrine disorders apart from T2DM, consumption of alcohol or recreational drugs within the past 3 months, acute coronary syndrome, stroke, or transient ischemic attack in the past 6 months, ongoing use of anti-inflammatory drugs (e.g., NSAIDs, steroids) in the 2 weeks before treatment, diagnosis of HIV or neurodegenerative diseases (e.g., Alzheimer's, Parkinson's), and the addition of any other diabetes medications during the study.

Sampling method

Non-probability purposive sampling was used to select participants. Patients were identified based on their eligibility for inclusion in the study and willingness to provide written informed consent.

Sample size calculation

The sample size was calculated using a 95% confidence level, 80% power, and 0.5 effect size. Based on these parameters and previous study [18], the required sample size was 70 patients for each group.

Study protocol

After recruitment, blood tests, ultrasound, and MRI were used to assess liver function and measure hepatic steatosis before and 3, and 6 months after initiating Empagliflozin treatment. According to evidence imaging methods are considered reliable methods for diagnosis and quantification of hepatic steatosis [19].

Clinical and laboratory measurements

The study included patients aged 20 to 70 years diagnosed with T2DM who visited Laghman Hakim Hospital for treatment with Empagliflozin in 2021. At baseline, patients' demographic and clinical data, including anthropometric measurements (height and weight), were collected.

Weight: Measured with minimal clothing and without shoes using a digital scale.

Height: Using a tape measure, measure in a standing position without shoes.

In addition to anthropometric data, blood samples were collected to assess the following laboratory markers at baseline and after 6 months of treatment:

HbA1c, Fasting Blood Sugar (FBS), Insulin, HDL, LDL, Total Cholesterol, Triglycerides (TG), ALT, AST, Alkaline Phosphatase (Alkp), Gamma-glutamyl transferase (GGT), Total Bilirubin (Bili), Direct Bilirubin (Direct Bili), and Albumin (Alb).

Liver imaging

Ultrasound and MRI were used to assess the degree of hepatic steatosis.

Ultrasound: Performed with a Hitachi EUB 405 machine using a 3.5 MHz convex probe. A radiologist performed the procedure blinded to the study's objectives and the paraclinical results. Hepatic steatosis was semi-quantitatively classified as 0 (no steatosis), 1 (mild), 2 (moderate), or 3 (severe), based on increased echogenicity, liver-kidney echogenicity differences, deep liver echo penetration, and liver vascular clarity.

MRI: A 1.5 Tesla MRI scanner was used to quantify liver fat. Using chemical shift imaging sequences, fat content was measured with both out-of-phase and in-phase sequences, with the fat in liver cells displayed as bright initially and suppressed. Fat content was quantified in a specific region of interest (ROI) using MRI software.

These measurements were applied for all individuals.

Inter-observer concordance was assessed for liver imaging evaluations to ensure consistency in imaging interpretation.

Biomarker analysis and insulin resistance calculation

Blood samples were analyzed for various biomarkers to assess the metabolic status of the patients. Insulin resistance was calculated using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) formula: [Fasting Insulin (μg/ml)]*[Fasting Glucose (mmol/l)]/22.5.

Study timeline and follow-up

The study was conducted over a 6-month period, with assessments at baseline (before Empagliflozin treatment) and at 3- and 6-months following treatment initiation. Healthcare staff monitored all patients throughout the study period, ensuring consistent application of treatment and care protocols across the study groups.

Statistical analysis

All the data were analyzed in SPSS 26 software, and their normal distribution was evaluated using the Kolmogorov-Smirnov test. Continuous and categorical data were reported by mean (standard deviation) (SD) and frequency (%), respectively. A binomial regression model was utilized for risk difference (RD) estimation and 95%CI and interpreted clinically by Rahlfs et al. (2019) [20]. Logistic and ordinal logistic regression were fitted to estimate the odds ratio (OR) and confidence interval of 95% for binary and ordinal outcomes controlling for baseline measurement, respectively. ORs were interpreted based on the zones introduced by Olivier et al. [21]. Mean difference (MD) with % a 95-confidence interval for continuous outcomes was calculated for post-intervention (months 3 and 6) using multiple linear regression to adjust baseline values and other factors (if necessary). In addition, standardized mean difference (SMD) with a 95% confidence interval was utilized to estimate the efficacy [22], which is interpreted as no effect ($0 < SMD < 0.2$), small effect ($0.2 < SMD < 0.5$), moderate effect ($0.5 < SMD < 0.8$), and large effect ($SMD > 0.8$). The Number Needed to Treat (NNT) was computed using an online tool for all metrics [23]. Intention-to-treat (ITT) analysis was used for sensitivity analysis. Analysis used STATA 14, logit, ologit, regress, esizereg, binreg, and mi (for missing imputation) commands. The significance level was set to 0.05.

Results

A total of 140 patients were enrolled and randomly assigned to either the intervention or control group. However, 21patients lost to follow-up due to COVID-19-related issues. Finally, a total of 119 patients (Intervention ($N = 69$), Control ($N = 50$)) were participated. About 54.29% of participants in the intervention group and 45.71% in the control group were men. The mean (SD) age of participants in the intervention group was 46.32 (8.11), while in the control group it was 52.56(10.26).

One patient from the intervention group and 20 patients from the control group were excluded from the study due to COVID-19-related issues (Fig. 1). The two groups had no statistically significant differences in baseline demographic characteristics (Table 1).

As shown in Table 2, the intervention group demonstrated a greater reduction in the grade of fatty liver compared to the control group, based on MRI and ultrasound assessments. In the intervention group, 12 patients (17.5%) had a reduction in fatty liver grade from grade 3 to grade 1, while only 3 patients (6%) in the control group experienced the same reduction. The odds of an increase in fatty liver grade in the control group were 48 times higher (95% CI: 15.5, 148.5) based on MRI findings, and 52 times higher (95% CI: 15.2, 178.1) based on ultrasound findings, compared to the intervention group (NNT = 2, Table 3).

After six months, the risk of ALT abnormalities was significantly lower in the intervention group. The relative risk (RR) of ALT abnormalities was 0.72 (95% CI: 0.62, 0.84) times that of the control group, representing a significant difference of 0.27 (95% CI: -0.38, -0.16) between groups (Table 4). Furthermore, AST [RD (95% CI): -0.02 (-0.19, 0.15)] and alkaline phosphatase (ALKP) [RD (95% CI): -0.12 (-0.19, -0.04)] abnormalities were also significantly lower in the intervention group, both in terms of relative risk (RR) and risk difference (RD). However, the reduction in GGT abnormalities was not statistically significant.

In terms of absolute changes, Table 5 shows that ALT values significantly decreased in the intervention group compared to the control group, with a mean difference (MD) of -15.33 (95% CI: -18.8, -11.88). Additionally, significant decreases were observed in the intervention group for AST [MD: -12.82 (-15.5, -10.13)], GGT [MD: -15.58 (-18.68, -12.47)], and systolic blood pressure (SBP) [MD: -6.31 (-8.65, -3.97)]. The intent-to-treat (ITT) analysis showed that the results were not influenced by any loss-to-follow-up cases, as demonstrated in Table 4.

Discussion

The present study evaluated the effect of empagliflozin on NAFLD-related parameters in patients with T2DM. Findings revealed that there was a significant reduction in liver fat grade in the intervention group compared to the control group. The odds of worsening fatty liver in the control group were 48 times higher on MRI and 52 times higher on ultrasound, compared to the intervention group. After 6 months, the intervention group showed significantly lower risks for ALT, AST, and Alkp abnormalities. Liver enzyme levels and SBP decreased significantly in the Empagliflozin group.

According to the last version of consensus statement on new fatty liver disease nomenclature when there is at least 1 of 5 cardiometabolic risk factors, NAFLD can replaced with metabolic dysfunction–associated steatotic liver disease (MASLD) [24]. In this study, since all patients suffered from diabetes, so they had 1 cardiometabolic risk factor and we considered it as MASLD. However, there is no direct investigation of NAFLD/MASLD in this context. Instead, the focus is on assessing related

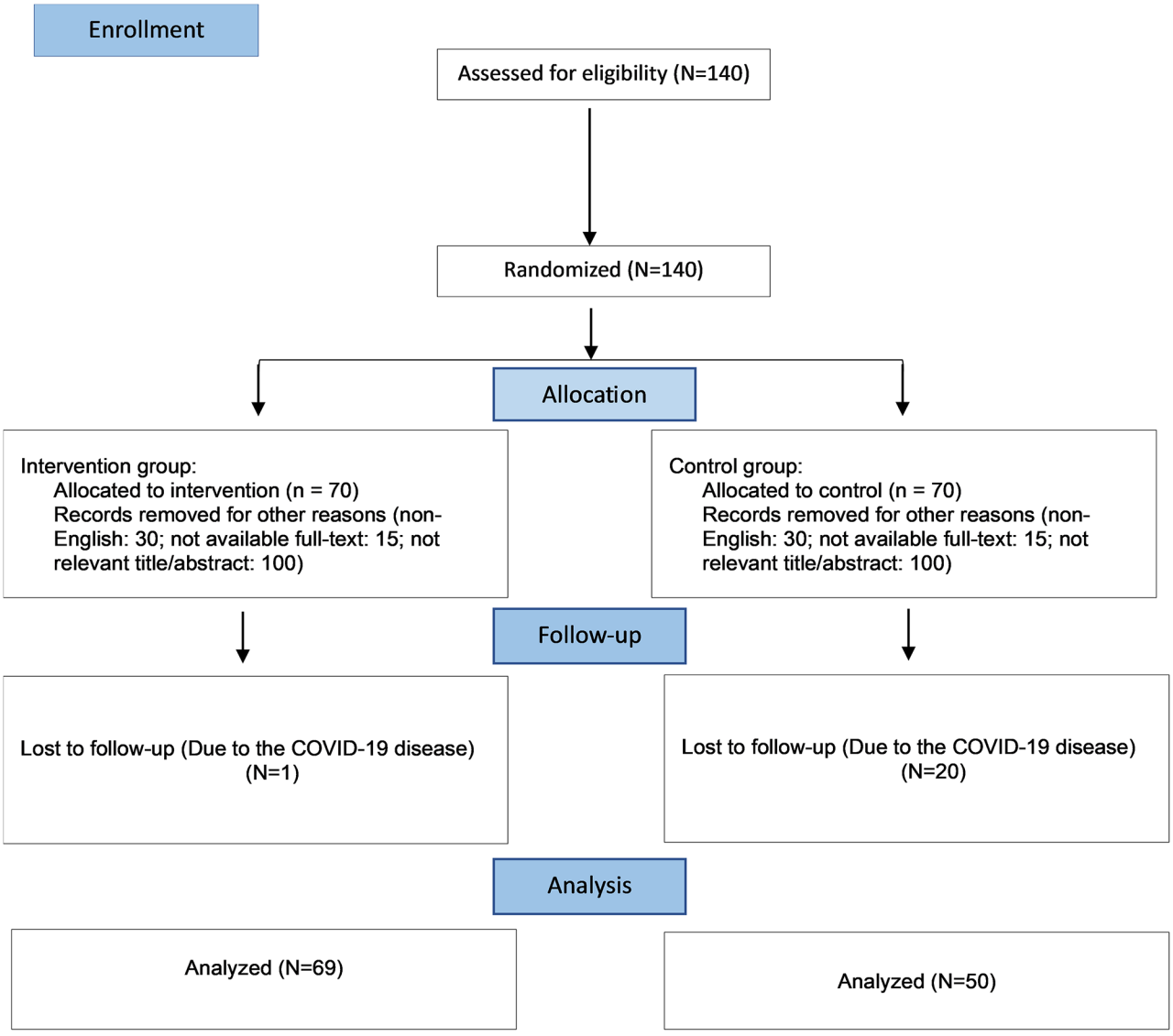

Fig. 1 CONSORT flow diagram

Table 1 Demographic characteristics of the patient's baseline

	Intervention (*N* = 69)	**Control (*N* = 50)**
Sex (men), n (%)	38 (54.29)	32 (45.71)
	Mean (SD)	
Age	46.32 (8.11)	52.56(10.26)
BMI	32.18 (4.24)	31.13 (6.05)
SBP	118.19 (11.42)	121.10 (10.11)
DBP	73.55 (10.58)	74.50 (9.05)
FBS	123.78 (26.52)	113.06 (13.15)
HbA1c	6.59 (0.72)	6.63 (0.44)
Insulin level	17.80 (6.70)	12.84 (4.52)

parameters in patients with diabetes. This means that while factors associated with NAFLD/MASLD (such as liver enzymes, metabolic markers, or imaging findings) may be evaluated, there study does not aim to diagnose or directly investigate these liver diseases themselves.

However, the present findings contrast with the results of a meta-analysis by Tang et al. (2022), which included three randomized controlled trials (RCTs) involving 212 patients. In this analysis, empagliflozin treatment showed no significant improvement in several key measures related to NAFLD, including the controlled attenuation parameter (CAP) score, hepatic steatosis, liver stiffness measurement (LSM) score, as well as liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), along with markers of lipid metabolism such as low-density lipoprotein (LDL)

Table 2 Fatty liver grade from MRI and sonography for control and intervention groups before the study and after six months

After									
Before		**Intervention**				**Control**			
		G0	**G1**	**G2**	**G3**	**G0**	**G1**	**G2**	**G3**
MRI	G0	2 (3)	0	0	0	0	0	0	0
	G1	1 (1.5)	1 (1.5)	0	0	0	0	0	0
	G2	14 (20)	29 (42)	1 (1.5)	0	0	11 (22)	29 (58)	0
	G3	5 (7)	12 (17.5)	4 (6)	0	0	3 (6)	4 (8)	3 (6)
		G1	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**
Sonography	G1	0	0	0	0	0	0	0	0
	G2	14 (20)	0	0	0	3 (6)	9 (18)	0	0
	G3	31 (45)	17 (24.5)	1 (1.5)	0	0	26 (52)	12 (24)	0
	G4	4 (6)	1 (1.5)	1 (1.5)	0	0	0	0	0

Table 3 Odds ratio (95CI%) of increase of fatty liver grade using ordinal logistic regression adjusted for baseline values

Variable			Intervention	Control	OR*(%95CI)
MRI	Baseline				-
		G0	2 (3)	0	
		G1	2 (3)	0	
		G2	44 (64)	40 (80)	
		G3	21 (30)	10 (20)	
	Month 6				48 (15.5, 148.5) NNT = 2
		G0	22 (32)	0	
		G1	42 (61)	14 (28)	
		G2	5 (7)	33 (66)	
		G3	0	3 (6)	
Sonography	Baseline				-
		G1	0	0	
		G2	12 (24)	14 (20)	
		G3	38 (76)	49 (71)	
		G4	0	6 (9)	
	Month 6				52 (15.2, 178.1) NNT = 2
		G1	49 (94)	3 (6)	
		G2	18 (34)	35 (66)	
		G3	2 (14)	12 (86)	
		G4	0	0	

and triglycerides (TG). According to this meta-analysis, empagliflozin treatment did not significantly improve these parameters in patients with NAFLD, suggesting that its effects might be less pronounced or inconsistent in certain patient populations or study settings. The discrepancies between the present study and the meta-analysis may be attributed to differences in study design, sample size, treatment duration, or patient populations' baseline characteristics. Additionally, variability in the diagnostic tools and endpoints used to assess liver function across studies could explain the conflicting results.

The results showed a greater reduction in the grade of fatty liver, liver enzyme abnormalities, and certain cardiovascular parameters in the empagliflozin group compared to the control group. These findings are consistent with prior studies that have suggested a beneficial effect of sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin, in the treatment of NAFLD [11, 16]. The proposed mechanisms for this effect include improved insulin sensitivity, reduced liver fat content, and anti-inflammatory effects. Additionally, empagliflozin's ability to reduce the burden of systemic glucose and associated metabolic disturbances likely plays a role in its positive impact on liver function in patients with T2DM and NAFLD [25].

Kuchay et al. (2018) [16] evaluated the impact of Empagliflozin on liver fat in patients with T2DM and NAFLD. They reported a significant difference between the two groups in the change in serum ALT levels, while the differences in AST and GGT levels were nonsignificant.

Also, results showed that the reduction in the risk of abnormal GGT in the intervention group compared to the control group was not statistically significant and had a small and uncertain effect. Also, findings demonstrate that the use of the drug led to a significant reduction in GGT levels. However, to assess whether this reduction is clinically meaningful, it should be evaluated in terms of the Minimum Clinically Important Difference (MCID), as reported in other studies. Additionally, a significant effect size (SMD) was observed for the intervention's impact on GGT, with the results remaining robust over a six-month period.

The MCID represents the smallest change in a treatment outcome that would be considered meaningful from a clinical perspective. For GGT, there is currently limited consensus on what constitutes a clinically important reduction, as values vary depending on the population studied, the baseline severity of liver disease, and the clinical context. In studies of NAFLD and T2DM, reductions in GGT levels are often used as an indirect marker of improvement in liver health. However, for these changes to be deemed meaningful, they must be evaluated in the context of MCID values derived from future similar clinical studies.

Table 4 Adjusted risk ratio (RR) with %95CI and adjusted risk difference (RD) with %95CI for biomarkers of fatty liver addition to sensitivity analysis via ITT approach

Variable			Group		Per protocol		ITT*	
			Intervention (*N* = 69)	Control (*N* = 50)	RR (95%CI)	RD (95%CI)	RR (95%CI)	RD (95%CI)
Alt	Baseline	Normal	0	0	-	-	-	-
		Abnormal	70 (50)	70 (50)	-	-	-	-
	Month 3	Normal	8 (89)	1 (11)	-	-	-	-
		Abnormal	61 (44.55)	49 (55.45)	0.90 (0.82, 0.99)	-0.10 (-0.18, -0.01)	0.16 (0.02, 1.29)	-0.10 (-0.18, -0.01)
	Month 6	Normal	20 (95.24)	1 (4.76)	-		-	-
		Abnormal	49 (50)	49 (50)	0.72 (0.62, 0.84)	-0.27 (-0.38, -0.16)	0.05 (0.006, 0.38)	-0.27 (-0.38, -0.16)
Ast	Baseline	Normal	15 (30.61)	34 (69.39)	-	-	-	-
		Abnormal	54 (60)	36 (40)	-	-	-	-
	Month 3	Normal	44 (58.67)	31 (41.33)	-	-	-	-
		Abnormal	25 (57)	19 (43)	0.95 (0.59, 1.53)	-0.02 (-0.19, 0.15)	0.93 (0.45, 1.9)	-0.02 (-0.19, 0.15)
	Month 6	Normal	59 (65.56)	31 (34.44)	-		-	-
		Abnormal	10 (34.48)	19 (65.52)	0.38 (0.19, 0.75)	-0.24 (-0.39, -0.08)	0.28 (0.12, 0.67)	-0.23 (-0.38, -0.08)
Alkp	Baseline	Normal	7 (100)	0	-	-	-	-
		Abnormal	62 (60)	50 (40)	-	-	-	-
	Month 3	Normal	10 (100)	0	-	-	-	-
		Abnormal	59 (54)	50 (46)	0.86 (0.77, 0.94)	-0.14 (-0.23, -0.06)	0.90 (0.88, 0.92)	-0.10 (-0.12, -0.08)
	Month 6	Normal	8 (100)	0	-	-	-	-
		Abnormal	61 (55)	50 (45)	0.88 (0.81, 0.96)	-0.12 (-0.19, -0.04)	0.88 (0.86, 0.91)	-0.11 (-0.14, -0.09)
GGT	Baseline	Normal	22 (31)	49 (70)	-	-	-	-
		Abnormal	47 (69.12)	21 (30.38)	-	-	-	-
	Month 3	Normal	49 (57)	37 (43)	-	-	-	-
		Abnormal	20 (60.61)	13 (39.39)	1.11 (0.61, 2.02)	0.03 (-0.13, 0.19)	1.16 (0.51, 2.63)	0.03 (-0.13, 0.19)
	Month 6	Normal	58 (61)	37 (39)	-	-	-	-
		Abnormal	11 (54)	13 (46)	0.61 (0.30, 1.25)	-0.10 (-0.25, 0.05)	0.54 (0.22, 1.33)	-0.10 (-0.25, 0.05)

Normal Alt for male: 29–33, for female: 19–25, Normal Ast for male: 10–40, for female: 9–32, Normal Allk.p for men: 45–115, for women: 30–100, Normal GGT for male: 8–61, for female: 5–36, *Intention-to-treat analysis using multiple imputation (*N* = 70 in each group)

The relative risk of ALT abnormalities was significantly lower in the empagliflozin group (RR: 0.72), indicating a substantial reduction in the risk of liver enzyme abnormalities. A significant reduction in ALT levels was observed with empagliflozin, with the effect becoming conclusive after 6 months of treatment. The mean difference in ALT was − 6.58, indicating that the intervention group had lower ALT levels, and this difference was statistically significant. However, it should be compared with the MCID from similar studies to determine whether this difference is clinically meaningful. In the meta-analysis by Zhang et al. [11], MCID in ALT was − 3.30 (MD: -3.30, 95% CI: -8.85 to 2.26, $p = 0.24$, $I^2 = 0\%$). Since the mean difference in our study was larger than that observed in Zhang et al., this suggests that our intervention led to a clinically significant reduction in ALT levels.

The most significant finding in this study is the greater reduction in fatty liver grade observed in the empagliflozin group compared to the control group. This

Table 5 Adjusted MD (%95CI) and adjusted SMD (%95CI) for biomarkers of fatty liver

		Intervention (*N* = 69)	Control (*N* = 50)		
		Mean (SD)		MD (95%CI)	SMD (%95CI)
ALT*	Baseline	71.33 (49.35)	47.52 (7.46)	-	-
	Month 3	41.48 (2.12)	43.46 (1.08)	-6.58 (-11.35, -1.82)	-0.47 (-0.84, -0.1)
	Month 6	30.16 (1.33)	42.9 (1.12)	-15.33 (-18.8, -11.88)	-1.73 (-2.16, -1.31)
AST*	Baseline	46.74 (14.14)	42.54 (11.61)	-	-
	Month 3	35.65 (1.24)	39.42 (1.46)	-5.97 (-8.83, -3.1)	-0.6 (-0.96, -0.22)
	Month 6	28.34 (0.99)	39.2 (1.54)	-12.82 (-15.5, -10.13)	-1.46 (-1.86, -1.05)
ALKp*	Baseline	186.91 (66.43)	197.98 (40.30)	-	-
	Month 3	176.52 (7.32)	195.34 (5.53)	-10.28 (-2.2, 0.63)	-0.19 (-0.55, 0.17)
	Month 6	183.12 (7.67)	196.8 (5.57)	-4.1 (-13.08, 4.88)	-0.07 (-0.44, 0.29)
GGT*	Baseline	59.s55 (26.09)	42.07 (9.52)	-	-
	Month 3	41.91 (19.90)	42.68 (11.70)	-9.36 (-14.34, -4.38)	-0.74 (-1.11, -0.36)
	Month 6	34.01 (14.80)	41.48 (10.82)	-15.58 (-18.68, -12.47)	-1.97 (-2.41, -1.52)
SBP**	Baseline	118.19 (11.42)	120.86 (9.10)	-	-
	Month 3	115.62 (11.34)	120.60 (8.61)	-2.84 (-5.26, -0.42)	-0.43 (-0.80, -0.7)
	Month 6	112.32 (10.73)	120.70 (8.81)	-6.31 (-8.65, -3.97)	-0.87 (-1.25, -0.5)

*Adjusted MD and SMD for baseline measurement using multiple linear regression

** Adjusted SMD for baseline measurement and BMI change using multiple linear regression

represents a substantial advantage for empagliflozin, with the odds of an increase in the fatty liver grade being 48 to 52 times higher in the control group than in the empagliflozin group. The number needed to treat (NNT) to achieve one additional patient with a reduction in fatty liver grade is 2. In other words, for every two individuals receiving the intervention, one will experience a successful outcome—a reduction in fatty liver grade confirmed by MRI.

Both AST and ALKP values showed significant reductions, further supporting the beneficial effects of empagliflozin on liver health. However, although a reduction in the risk of abnormality in the alkaline factor was observed and was statistically significant, the clinical effectiveness of the intervention was small and lacked certainty. Incontinent with our findings, the study by Komiya et al. (2016) demonstrated that the use of SGLT2 inhibitors in patients with type 2 diabetes and NAFLD led to improvements in serum AST and GGT levels, regardless of changes in body weight [26].

In addition to improvements in liver function, the empagliflozin group showed a significant reduction in systolic blood pressure (SBP), with a mean difference (MD) of -6.31 mmHg (-8.65, -3.97) and a standardized mean difference (SMD) of -0.87 (-1.25, -0.5), suggesting a moderate to large effect size for the intervention. However, the clinical relevance of this reduction remains uncertain. This outcome aligns with the established effects of SGLT2 inhibitors on blood pressure, likely mediated by mechanisms such as osmotic diuresis, natriuresis, and potential improvements in vascular function [27]. Given the high prevalence of hypertension in patients with T2DM and NAFLD, the observed reduction in SBP provides an important additional benefit of empagliflozin treatment.

Limitations and strengths

One of the key strengths of this study is the use of both MRI and ultrasound to assess liver fat content, providing a robust and accurate measure of changes in liver health. These non-invasive imaging techniques offer a more reliable assessment of liver fat than conventional liver biopsy, making them suitable for clinical practice. Furthermore, the study's randomized controlled design strengthens the findings' validity and supports empagliflozin's potential efficacy in improving liver outcomes in patients with T2DM.

While the study presents promising results, several limitations should be considered. First, the sample size of 140 patients, with 21 patients lost to follow-up due to COVID-19-related issues, may limit the generalizability of the findings. Additionally, the study duration of six months may not be sufficient to capture long-term effects or potential adverse events associated with empagliflozin therapy. Future studies with larger sample sizes and longer follow-up periods must confirm empagliflozin's long-term efficacy and safety in patients with T2DM and NAFLD-related parameters. Moreover, while this study focused on liver function and related metabolic parameters, it did not assess other important outcomes such as liver histology (e.g., degree of fibrosis) or clinical outcomes like cirrhosis or hepatocellular carcinoma.

Conclusion

The findings of our study provide compelling evidence for the beneficial effects of empagliflozin in patients with T2DM and NAFLD. Empagliflozin treatment significantly improved liver fat content, liver enzyme levels, and systolic blood pressure, suggesting its potential as a therapeutic option for managing NAFLD-related parameters in this high-risk population. Further studies with larger sample sizes, longer follow-ups, and incorporating liver biopsy or elastography to assess liver fibrosis and more comprehensive clinical endpoints will be critical in determining the overall impact of empagliflozin.

Supplementary Information

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Supplementary Material 1

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Author contributions
F.S. and A.E. wrote the main manuscript text, and L.G. prepared figures and tables. S.N. and S.K. reviewed the manuscript, and all authors approved it.

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Data availability
Data will be available upon request from the corresponding author and All data generated or analyzed during this study are included in this manuscript.

Declarations

Ethics approval and consent to participate
This study received ethical approval from the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ethical code: IR.SBMU.MSP.REC.1400.287) and this study was conducted under the Declaration of Helsinki. After being informed of the research's benefits and risks, participants signed written consent. Registered retrospectively in the Iranian Registry of Clinical Trials (IRCT20210811052150N1) on April 16,2023 Access at https://irct.behdasht.gov.ir/search/result?query=IRCT20210811052150N1.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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