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The effects of empagliflozin on diuresis and natriuresis in patients with type 2 diabetes mellitus and liver cirrhosis

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Abstract

Background We investigated the short-term diuretic and natriuretic effect of empagliflozin, a sodium-glucose linked transporter 2 inhibitor, in patients with cirrhosis and type 2 diabetes mellitus (T2DM).

Methods This was a prospective, single-arm study including 30 patients with T2DM and cirrhosis (Child-Pugh class A/B). Participants received empagliflozin 10 mg for 15 days while continuing their standard treatment. Clinical and biochemical parameters, and urinary samples, using 24-h urine collection, were recorded before and after treatment. Twenty-seven patients continued empagliflozin for 6 months and were assessed for glycemic control and renal function.

Results Empagliflozin increased median daily urine volume by 475 mL (P=0.010) and fractional sodium excretion (FE_{Na}) by 16% at day 15 (P=0.030), but the 8 mmol/L increase in 24-h sodium excretion was not significant. Empagliflozin also reduced body weight (-0.8 kg, P<0.001) and systolic blood pressure (-4 mmHg, P=0.029). Glycemic control remained unremarkable at day 15, but improved at 6 months (baseline vs. 6 months: fasting glucose 146 vs. 116 mg/dL, P=0.016; glycosylated hemoglobin 6.2% vs. 6%, P=0.011). Compared to baseline (89.1±20.6 mL/min/1.73m^2, estimated glomerular filtration rate declined numerically but not statistically significantly at day 15 (85.2±21.8, P=0.056 and at 6 months (82.8±23.7, P=0.035. No serious adverse events were noticed.

Conclusions Up to 6 months' empagliflozin administration in patients with cirrhosis and T2DM seems safe and increases urine output and FE_{Na}, but its impact on renal function requires further investigation. Larger randomized controlled trials are needed to confirm its long-term efficacy and safety in this setting.

Keywords Cirrhosis, diabetes, empagliflozin, diuresis, natriuresis

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Introduction

Liver cirrhosis frequently coexists with impaired glucose metabolism disorders, as approximately one third of such patients exhibit impaired glucose tolerance (IGT) and another third present with overt diabetes [1]. On the other hand, the presence of hyperglycemia severely alters the prognosis in this setting. However, treatment options for patients with cirrhosis and type 2 diabetes mellitus (T2DM) remain limited, as many of the drugs used in T2DM are contraindicated in patients with advanced liver disease [2].

Sodium-glucose linked transporter 2 inhibitors (SGLT2-i) are a class of glucose-lowering medication that acts on the renal proximal convoluted tubule, independently of insulin, by promoting glycosuria and natriuresis, contributing to glycemic control by reducing HbA1c by 0.6-1% [3]. Beyond their glucose-lowering effects, SGLT2-i have been shown to ameliorate outcomes in heart failure (HF), by reducing all-cause mortality and hospitalization in patients with HF and either preserved or reduced ejection fraction, regardless of T2DM [4]. The mechanism of their cardioprotective action has not been yet fully elucidated. The reduction in hospitalizations for HF could be related to a reduction in preload and/or afterload, and improvement in left ventricular contractility [5],

Conflict of Interest: None

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while it appears that the positive outcomes in HF come from reducing preload by increasing, at least, short-term natriuresis and osmotic diuresis. Congestive HF and decompensated cirrhosis share some common pathophysiological features and pharmacological treatment. In both entities, though for different reasons, there is a reduction in effective blood volume, which leads to activation of the renin–angiotensin–aldosterone system, sympathetic nervous system and antidiuretic hormone secretion [6]. In HF, loop diuretics (furosemide, torasemide and bumetanide) are routinely used to treat volume overload [7], while mineralocorticoid receptor antagonists (MRAs) are a first-line treatment option in HF with reduced ejection fraction [8]. Similarly, spironolactone is also a first-line option in decompensated cirrhosis with ascites and/or edema, whereas furosemide is used on top of spironolactone in cases of ascites unresponsive to salt-restricted diet and MRAs [9].

Based on the beneficial effects of SGLT2-i in HF, and the similarities in pathophysiological mechanisms between those 2 clinical conditions, one could hypothesize that SGLT2-i could also be useful in cirrhosis, either at the initial compensated stage, for the modification of early renal hemodynamic disorders, or at more advanced stages, for its diuretic effects in improving edema and ascites. In fact, retrospective studies showed that SGLT2-i may decrease the probability of liver decompensation and mortality in patients with compensated cirrhosis and T2DM [10,11]. Thus, the aim of this study was to investigate the short-term diuretic and natriuretic effect of the SGLT2-i empagliflozin in patients with cirrhosis and T2DM on top of their ongoing medication.

Patients and methods

Study design and patient population

This was a prospective, single-arm, open-label study, which recruited outpatients with cirrhosis and T2DM between December 2020 and March 2024. Patients were enrolled from either of our outpatient liver and/or diabetes clinics if they fulfilled all the inclusion and exclusion criteria. Inclusion criteria were age ≥18 years, and an established diagnosis of both T2DM and compensated or decompensated cirrhosis (Child-Pugh class A or B) of any etiology. Patients were excluded if they were already receiving SGLT-i at screening, had screening systolic arterial pressure <90 mmHg, a medical history of diabetic ketoacidosis, baseline estimated glomerular filtration rate (eGFR-CKD-EPI Cre 2021) <25 mL/min/1.73m^2, Child-Pugh class C decompensated cirrhosis, hepatocellular carcinoma or any other active malignancy.

Although SGLT2-i have also been approved for heart failure and chronic kidney disease, only patients with T2DM were included in this study, since T2DM was the primary clinical indication for empagliflozin at the study design and initiation in 2020.

The study protocol was approved by the ethics committee of the Institutional Review Board of our Hospital and the study was conducted according to the principles outlined in the Declaration of Helsinki. All patients included in the study provided written informed consent.

Definitions

Liver cirrhosis was defined by histological findings and/or liver stiffness >14 kPa by transient elastography [12] (FibroScan®, Echosens). Decompensated cirrhosis was defined by the presence of any decompensating event, such as ascites, variceal bleeding, hepatic encephalopathy and/or jaundice of non-obstructive etiology. T2DM was defined according to local and international guidelines by the presence of hyperglycemia in fasting blood glucose (FBG >125 mg/dL), oral glucose tolerance test (OGTT-glucose >200 mg/dL), HbA1c ≥6.5% or symptomatic hyperglycemia >200 mg/dL in the past, or using any glucose-lowering medication [13].

Study procedures and measurements

All patients received 10 mg of empagliflozin once daily for 15 consecutive days, on top of their ongoing treatment. Moreover, in accordance with cirrhosis guidelines, patients were asked to follow a low-salt diet. Demographic and clinical characteristics were collected before and after the intervention. Weight and height were measured on days 0 and 15, using an automated scale and a calibrated stadiometer, with the patient wearing light clothing; body mass index (BMI) was calculated as the ratio of weight (kg) to height (m) squared. Blood pressure measurements were performed 3 times, 1 minute apart, in the sitting position, using a commercially available, fully automated, oscillometric sphygmomanometer; the recorded value was the mean of the last 2 measurements.

Blood was drawn and a 24-h urine collection was performed at the beginning of the study (day 0) and during the end of the empagliflozin administration (day 15). The 24-h urine collection was performed according to the international guidelines [14]. The first morning urination of the first collection day was discarded in the toilet. Subsequently, the content of each urination was stored in the special urination container. The collection was completed with the collection of the first morning urine of the second day. Patients with 24-h urine volume <500 mL and/or urine creatinine <5 mg/kg were

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excluded because of inadequate urine collection. In addition, blood sampling was performed in the morning and after the patient had fasted for at least 8-10 h.

After the 15-day period, continuation of empagliflozin was based on the attending physician's judgment. Patients who continued treatment with 10 mg empagliflozin for 6 months were contacted by telephone and returned to the study center for additional assessments.

Fasting glucose, serum and urine creatinine were measured on an automatic analyzer (Olympus AU560, Hamburg, Germany). Glycated hemoglobin (HbA1c) was measured using a latex–immunoagglutination–inhibition method (Bayer HealthCare LLC, Elkhart, IN, USA) with a non-diabetic range of 4.0-6.0% (20-42 mmol/mol). eGFR was calculated using the CKD-EPI Creatinine 2021 equation [15]. Fractional excretion of sodium (FE_{Na}) was calculated according to the standard formula: $FE_{Na}= 100x(U_{Na}\times P_{Cre})/(P_{Na}\times U_{Cre})$, where U_{Na} and U_{Cre}, P_{Na} and P_{Cre}, are the urinary and plasma concentrations of sodium and creatinine, respectively. In patients receiving diuretic treatment, the medication remained stable during the study period. Similarly, the degree of chronic kidney disease, as assessed by eGFR category, remained stable throughout the study period. All patients had a capillary blood ketone test with a stick before drug initiation and at the end of 15 days.

Statistical analysis

All data were collected into an electronic database for statistical processing. The Statistical Package for the Social Sciences (IBM® SPSS® Statistics 29.0, SPSS Inc, IBM, Chicago, IL, USA) was used for the statistical analysis. Initially, we checked for normality of the variables using the Shapiro-Wilk test. Quantitative variables with normal distribution are presented as mean values ± standard deviation, while variables without normal distribution are presented as median values (interquartile range). Parametric tests were used for comparisons of variables with a normal distribution between groups, while non-parametric tests were used for similar comparisons of variables with a non-normal distribution. The level of statistical significance was defined as $P<0.05$.

The Friedman test was used to analyze changes in fasting glucose, HbA1c, and serum creatinine levels across the 3 time points, as these variables were not normally distributed. In contrast, repeated measures ANOVA was applied to assess changes in eGFR, which followed a normal distribution and met parametric assumptions. Where significant differences were found, Wilcoxon signed-rank tests were performed for pairwise comparisons between time points, with the Bonferroni correction applied. With 3 comparisons per variable (baseline vs. post-intervention, post-intervention vs. 6 months, and baseline vs. 6 months), the significance threshold was adjusted to $P<0.0167$. For normally distributed variables, such as eGFR, repeated measures ANOVA was used to assess changes over time, with *post hoc* pairwise comparisons conducted as appropriate.

Results

The baseline characteristics of the study participants are summarized in Table 1. In total, 33 patients were initially screened and 30 subjects were finally included. Their mean age was 63.3±8.5 years and 73% of them were males. The mean duration of T2DM was 12.3±10.7 years and the mean duration of cirrhosis was 7.0±6.9 years. The median HbA1c was 6.2% (5.8-7.9 indicating a well-controlled population.

Table 1 Baseline characteristics of 30 patients with cirrhosis and diabetes

Baseline characteristics	Total study population (N=30)
Age, years	63.3±8.5
Male sex, n (%)	22 (73)
Body mass index, kg/m^2	27.4 (24.5-32.1)
Weight, kg	80.7 (73.4-95.0)
Height, cm	171.8±10
Vital signs	
Systolic pressure, mmHg	126.9±17.4
Diastolic pressure, mmHg	71.1±12.2
Heart rate, bpm	68.0 (63.0-74.5)
Disease duration	
Diabetes duration, years	12.3±10.7
Cirrhosis duration, years	7.0±6.9
Cause of cirrhosis, n	
Metabolic associated steatotic liver disease	11
Alcohol abuse	7
Chronic hepatitis B virus infection	3
Chronic hepatitis C virus infection	4
Other	4
Cryptogenic	1
Disease severity	
Decompensated state, n (%)	18 (60)
Child-Pugh class A, n (%)	16 (53)
FIB-4 score	4.1±2.5
HbA1c, %	6.2 (5.8-7.9)
Renal function	
CKD-EPI mL/min/1.73m^2	89.5±20.0
eGFR <60 mL/min/1.73m^2 (%)	7 (23)
Cirrhosis medication, n (%)	
Diuretics	17 (57)
MRA	2
Loop	1
MRA+loop	14
b-blockers	25 (83)
Glucose-lowering medication, n (%)	28 (93)
Insulin	7
Non-insulin	16
Insulin+ non-insulin	5

Data are presented as mean ±standard deviation for normally distributed quantitative variables, and as median (interquartile range) for non-normally distributed variables

bpm, beats per min; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist

Cirrhosis was decompensated in 60% and compensated in 40% of patients; Child-Pugh class A was present in 60% and the median Child-Pugh score was 6 (5-7). The 3 major causes of cirrhosis were metabolic associated steatotic liver disease (MASLD) (n=11), alcohol abuse (n=7) and chronic viral hepatitis (hepatitis B/C virus: n=3/4). Mean baseline eGFR was 89.5±20.0 mL/min/1.73m^2 and chronic kidney disease (defined by eGFR <60 mL/min/1.73m^2) was present in 23% of patients.

In terms of baseline medication for cirrhosis, 57% of the patients were on diuretics, most of them receiving a combination of MRA, either spironolactone or eplerenone, and a loop diuretic; 2 of them had only MRA and 1 subject was only on loop diuretic. Most of them (83%) were also receiving a b-blocker. Additionally, 93% of patients were on glucose-lowering medication, with non-insulin therapies being the most prescribed agent, followed by insulin therapies and combination insulin/non-insulin regimens. Only 2 patients were under diet and exercise but no medication.

Effects of empagliflozin on anthropometric and hemodynamic parameters

All parameters before and at the end of the 15-day empagliflozin course are presented in Table 2. Comparing day 0 to day 15, there was a significant decrease in median body weight (from 80.7 to 79.9 kg, P<0.001) and BMI (27.4 to 26.6 kg/m^2, P<0.001). Mean systolic arterial pressure also decreased from day 0 to day 15 (from 126.9±17.4 to 122.7±13.9 mmHg, P=0.029, without significant changes in mean diastolic arterial pressure or heart rate.

Effects of empagliflozin on hematological and biochemical parameters

Empagliflozin resulted in an increase of mean platelet count at day 15 (from 122.8 to 129.6 x 10^3/L, P=0.004) and hematocrit (37.5% to 38.3%, P=0.030), but there was no significant change in hemoglobin levels or white blood cell count. There was also a decrease of alkaline phosphatase levels (112.5 U/L to 108.5 U/L, P=0.035), but the levels of the other liver enzymes remained stable. In addition, there was a significant reduction in uric acid levels (from 5.9 to 5.2 mg/dL, P=0.002) following 15 days of empagliflozin treatment.

Regarding glucose turnover following empagliflozin treatment, there was a trend for declining median HbA1c levels (6.2% to 6.1%, P=0.065), and only a numerical but non-significant decrease in median fasting glucose levels (147.5 to 136.0 mg/dL, P=0.170).

As expected, short-term administration of empagliflozin was followed by changes in renal parameters. In particular, median eGFR decreased (from 88.5 to 84.4 mL/min/1.72m^2,

Table 2 Effect of 15-day empagliflozin administration on anthropometric, hemodynamic and laboratory parameters in 30 patients with T2DM and cirrhosis

Parameters	Pre-empagliflozin	Post-empagliflozin	P-value
Weight, kg	80.7 (73.4-95.0)	79.9 (72.6-93.2)	0.001#
BMI, kg/m^2	27.4 (24.5-32.1)	26.6 (24.4-31.8)	0.001#
SAP, mmHg	126.9±17.4	122.7±13.9	0.029
DAP, mmHg	71.1±12.2	70.8±8.3	0.888
HR, bpm	68.0 (63.0-74.5)	71.0 (62.0-77.2)	0.982#
WBCs, 10^3/μL	5827.0±2148.5	5708.4±2142.2	0.589
Hemoglobin, g/dL	12.6±2.2	12.8±2.2	0.214
Hematocrit, %	37.5±6.0	38.3±6.2	0.030
Platelets, x10^6/μL	122.8±39.5	129.6±44.5	0.004
Fasting glucose, mg/dL	147.5 (120.5-183.0)	136.0 (113.8-160.0)	0.170#
HbA1c, %	6.2 (5.8-7.9)	6.1 (5.7-8.1)	0.065#
Urea, mg/dL	32.0 (27.0-50.3)	39.5 (32.5-46.3)	0.082#
Creatinine, mg/dL	0.82 (0.74-1.04)	0.85 (0.73-1.27)	0.006#
Uric acid, mg/dL	5.9±1.7	5.2±1.5	0.002
eGFR, mL/min/1.73m^2	88.5±20.0	84.4±21.8	0.001
Na+, mmol/L	138.0 (134.8-141.3)	138.0 (135.6-140.0)	0.693#
K+, mmo/L	4.4±0.5	4.4±0.4	0.964
AST, U/L	30.5 (24.8-43.0)	30.5 (24.8-41.5)	0.767#
ALT, U/L	23.0 (16.8-36.3)	23.5 (16.8-36.0)	0.910#
γ-GT, U/L	60.5 (33.3-122.0)	60.0 (31.8-116.5)	0.325#
ALP, U/L	112.5 (75.8-147.3)	108.5 (78.5-139.3)	0.035#
Tbil, mg/dL	1.00 (0.59-1.55)	1.13 (0.60-1.59)	0.510#
Dbil, mg/dL	0.46 (0.27-0.69)	0.44 (0.28-0.68)	0.580#
Albumin, g/L	40.4±6.4	40.9±6.8	0.177
Total protein, mg/dL	73.3±5.9	73.8±6.3	0.548
Total cholesterol, mg/dL	149.8±30.3	154.1±33.5	0.185
Triglycerides, mg/dL	94.0 (72.8-123.5)	105.0 (80.8-123.3)	0.078
HDL, mg/dL	49.5±13.0	48.4±14.6	0.380

(Contd...)

Table 2 *(Continued)*

Parameters	Pre-empagliflozin	Post-empagliflozin	P-value
LDL, mg/dL	78.6±26.1	80.9±26.5	0.427
Urine volume, mL	1900 (1530-2500)	2375 (1925-2700)	0.010#
FENa, %	0.71±0.48	0.87±0.70	0.030
Na urine 24h, mmol/L	120±63	128±75	0.440
Na urine, mmol/L	58.1 (33.6-85.1)	54.0 (33.3-83.3)	0.491#
K urine 24h, mmol/L	61.3±25.8	60.8±33.8	0.924
K urine, mmol/L	28.1 (21.9-39.0)	24.7 (17.6-33.6)	0.019#
Cl urine 24h, mmol/L	121±56	132±76	0.374
Cl urine, mmol/L	57±54	51±39	0.078#
Uric acid urine 24h, mmol/L	475.5 (379.8-608.0)	469.0 (372.8-616.3)	0.959#
Uric acid urine, mmol/L	22.9 (20.1-29.4)	19.6 (15.9-29.7)	0.021#
Na/K urine	2.16±1.29	2.29±1.39	0.574

Data are presented as mean ± standard deviation for normally distributed quantitative variables, and as median (interquartile range) for non-normally distributed variables. *P-values for comparisons with paired samples t-test. #P values for comparisons with related-samples Wilcoxon signed-rank test

T2DM, type 2 diabetes mellitus; BMI, body mass index; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; bpm, beats per minute; WBCs, white blood cells; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; AST, aspartate transaminase; ALT, alanine transaminase; γ-GT, gamma-glutamyltransferase; ALP, alkaline phosphatase; Tbil, total bilirubin; Dbil, diluted bilirubin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; FENa, fractional excretion of sodium

P=0.001), while serum creatinine levels increased from baseline to day 15 (0.82 to 0.85 mg/dL, P=0.006).

Effect of empagliflozin on urine parameters

Following the 15-day administration of empagliflozin, we observed clinically significant increases in both urine volume and FE_{Na}. Specifically, median daily urine volume increased by 475 mL from baseline to day 15 (1900 to 2375 mL, P=0.010) and FE_{Na} by 16% (0.71 to 0.87, P=0.030). In contrast, there were no significant differences in 24-h urine sodium and in spot urine sodium. Although there was a reduction in spot urine potassium by 3.4 mmol/L (from 28.1 to 24.7 mmol/L, P=0.019), there was no significant change in 24-h urine potassium. Uric acid urine spot sample also decreased by 3.3 mmol/L (P=0.021), but there was no decrease in the 24-h urine uric acid levels. First morning urine Na/K ratio, which is considered an alternative surrogate for 24-h urine Na, showed a trend towards an increase from baseline to day 15 (P=0.096). No significant changes were observed in 24-h urine chloride (P=0.574) after empagliflozin administration.

Safety profile

There were no statistically significant differences in serum electrolyte concentrations at baseline compared to the end of the study. Serum sodium (138.0 [134.8-141.3] at baseline versus 138.0 [135.6-140.0) mEq/L at day 15) and serum potassium (4.4±0.5 at baseline versus 4.4±0.4 mEq/L at day 15) remained unremarkable (P=0.693 and P=0.964 respectively). None of the study participants developed a genitourinary infection. In addition, no patient was found to be positive for blood ketones either before or at the end of the study, using blood ketone sticks.

Glycemic control and renal function at 6 months

Of the 30 patients initially enrolled in the study, 27 continued receiving 10 mg of empagliflozin for 6 months according to their attending physician's clinical judgment. In the 27 patients who continued empagliflozin treatment, fasting plasma glucose, HbA1c, serum creatinine and eGFR were assessed at baseline, day 15 and at 6 months (Table 3).

Because fasting glucose, HbA1c and creatinine were non-normally distributed, overall time effects were evaluated with the Friedman test; eGFR, which met normality assumptions, was analyzed with repeated-measures ANOVA. Significant within-subject variation was observed for fasting glucose (P=0.003), HbA1c (P=0.010), serum creatinine (P=0.002) and eGFR (P=0.031). Pairwise comparisons used Wilcoxon signed-rank tests or paired-samples t tests, with the Bonferroni adjustment (α=0.0167).

Regarding median fasting blood glucose, we observed a non-significant reduction from 146 mg/dL (121-182) at baseline to 131 mg/dL (113-145) on day 15 (P=0.170), and a significant decrease from day 15 to month 6 (116 mg/dL [98.0-124.0], P=0.016).

Furthermore, there was a trend for a decrease of median HbA1c from baseline (6.2% [5.8-7.0]) to day 15 (6.1% [5.7-6.8], P=0.065), as well as from day 15 to month 6 (6.0% [5.5-6.3], P=0.083), whereas the reduction from baseline to month 6 was significant (P=0.011).

Regarding renal parameters, median creatinine levels increased significantly from baseline (0.81 mg/dL [0.71-1.05]) to day 15 (0.85 mg/dL [0.74-1.27], P=0.006) and to month 6 (0.93 mg/dL [0.8-1.33], P=0.028), with a non-significant change from day 15 to month 6 (P=0.435). Interestingly, mean eGFR demonstrated a trend toward reduction from baseline (89.1±20.6 mL/min/1.73m^2) to day 15 (85.2±21.8 mL/min/1.73m^2; P=0.056), and a statistically significant decline from day 15 to month 6 (82.8±22.4 mL/min/1.73m^2; P=0.002). Although the decrease from baseline to month 6 (P=0.035) reached

Table 3 Longitudinal analysis of laboratory parameters at baseline, and after 15 days and 6 months under empagliflozin in 27 patients with cirrhosis and diabetes

Parameter	Baseline	2 weeks post	P-value*	6 months post	P-value**	P-value***
Fasting glucose, mg/dL P=0.003#	146.0 (121.0-182.0)	131.0 (113.0-145.0)	0.170¶	116.0 (98.0-124.0)	0.001¶	0.016¶
HbA1c, % P=0.010#	6.2 (5.8-7.0)	6.1 (5.7-6.8)	0.065¶	6.0 (5.5-6.3)	0.011¶	0.083¶
Creatinine, mg/dL P=0.002#	0.81 (0.71-1.05)	0.85 (0.74-1.27)	0.006¶	0.93 (0.8-1.33)	0.028¶	0.435¶
eGFR, mL/min/1.73m^2 P=0.031^	89.1±20.6	85.2±21.8	0.056∞	82.8±23.7	0.035∞	0.002∞

Data are presented as median (interquartile range) for non-normally distributed variables (fasting glucose, HbA1c=glycated hemoglobin, creatinine) and as mean ± standard deviation for normally distributed variables (eGFR=estimated glomerular filtration rate). *P-value: Baseline vs. 2 weeks post-intervention; **P-value: Baseline vs. 6 months post-intervention; ***P-value: 2 weeks vs. 6 months post-intervention. Overall comparisons across all 3 time points were performed using the Friedman test (# for non-parametric data) or repeated measures ANOVA (^ for parametric data). Pairwise comparisons were conducted using the Wilcoxon signed-rank test (¶) or paired t-test (∞), as appropriate. Statistically significant P-values are shown in **bold** (for pairwise comparisons **with Wilcoxon signed-rank test** the significance threshold was adjusted to P<0.0167 after Bonferroni correction)

nominal significance, it did not meet the Bonferroni-adjusted threshold (P<0.0167) and is therefore not considered statistically significant.

Discussion

To our knowledge, this is the first study to examine the diuretic and natriuretic action of empagliflozin in patients with cirrhosis and T2DM. Very few previous studies have evaluated the effects of SGLT2-i in this patient population; all studies but 1 were retrospective and thus had inherent limitations [10,11]. The only prospective study, which was published in 2024, highlighted the role of another SGLT2-I, dapagliflozin, in reducing ascites and diuretic dose in patients with cirrhosis and T2DM, but the treatment period was unclear and no urine data were reported [16]. On the other hand, the use of 24-h urine collection, which represents the gold standard for assessing sodium excretion, and the 6-month follow up under empagliflozin in most of our patients, increase the validity of our findings and provide clinical data about the long-term efficacy of an SGLT2-i in glycemic control and renal function in cirrhosis. The main findings of this study suggest that short-term administration of empagliflozin in subjects with cirrhosis and T2DM can significantly increase urine volume output and might contribute to natriuresis. In particular, 15-day empagliflozin administration increased FE_{Na}—which, however, is mainly used to differentiate between prerenal and intrarenal acute kidney injury, as an indication of tubular sodium handling [17], and less as an index of total sodium excretion. On the other hand, empagliflozin only led to a numerical increase in 24-h sodium excretion, which is widely regarded as the gold standard for measuring natriuresis [18]. At the same time, 15-day administration of the drug modestly reduced body weight, BMI and blood pressure. The observed reduction in body weight, by 0.8 kg, could be attributed mainly to the diuretic action of the drug, rather than to the loss of calories through glycosuria, since empagliflozin was initially administered for only 15 days. The observed reduction in blood pressure (4 mmHg) is consistent with the class effect of SGLT2-i in reducing blood pressure in T2DM patients [19]. Although concerns may be raised by the reduction of blood pressure in patients with cirrhosis, who are at risk for hemodynamic instability, all participants remained normotensive during the study period. Regarding heart rate, there was no difference between baseline and at day 15, but most of the study participants were receiving a b-blocker (n=25), possibly preventing any compensatory increase in heart rate.

Empagliflozin treatment resulted in additional potentially beneficial changes in hematological and biochemical parameters, including a modest increase in hematocrit and platelet count, and a reduction in uric acid levels, without significantly affecting key liver enzyme levels. Previous studies have also shown a beneficial effect of SGLT2-i on hematocrit. Proposed mechanisms involve increased erythropoiesis via hepcidin suppression, increased erythropoietin and hemoconcentration [20,21]. Given the short-term empagliflozin administration in our study, we think that the hematocrit increase could be attributed to hemoconcentration. The increase in platelet count was only modest, and probably not clinically significant, but further studies are needed to investigate whether there may be such a causal relationship. Several studies have shown that SGLT2-i reduce uric acid levels in individuals with T2DM and/or HF, mainly by ameliorating renal uric acid handling [22]. Moreover, data from the NHANES-I cohort study showed that increased uric acid levels are associated with a greater risk of cirrhosis-related complications [23]. All the above suggest that empagliflozin therapy may have side benefits in patients with cirrhosis and T2DM, having an overall favorable safety profile in this high-risk population.

Short-term intervention with 15-day administration of empagliflozin was insufficient to achieve a meaningful reduction in fasting blood glucose and HbA1c levels. However, considering that the lifetime of red blood cells is about 90 days, it is expected that the change in hemoglobin glycosylation would be clinically evident after a period of 3 months.

Indeed, empagliflozin led to a significant reduction in fasting blood glucose and HbA1c levels at 6 months, highlighting its potential efficacy in managing hyperglycemia in patients with cirrhosis and T2DM.

Renal function, as reflected by serum creatinine and eGFR, already showed an initial decline on day 15, which persisted at 6 months. The mechanism behind this decline is often attributed to afferent arteriole vasoconstriction, as has been previously described for SGLT2-i. This phenomenon is usually reversible, transient, tends to attenuate after 12 weeks and is protective in long-term administration by inhibiting glomerular hyperfiltration [24]. However, our data showed a continuous decline in eGFR, raising concerns about the overall renal safety of empagliflozin in cirrhotic patients. This warrants further investigation, particularly in cases with advanced liver disease.

Although the action of SGLT2-i in liver disease has been mostly studied in individuals with MASLD, showing promising results regarding amelioration of liver parameters and fat liver reduction [25], little is known about their action in liver cirrhosis. Data from large cardiovascular outcomes trials using SGLT2-i in subjects with T2DM and/or HF suggested that SGLT2-i have an acceptable safety profile, without any need for dose adjustment in patients with cirrhosis, except for canagliflozin which has not been studied in Child-Pugh C cirrhosis [26]. In our study, empagliflozin also demonstrated a favorable safety profile, with no significant electrolyte imbalance, no reported genitourinary infections, and no case of ketoacidosis. Thus, it is reassuring that empagliflozin had a good safety profile and did not exert adverse effects on hepatic function in our patients with compensated, or even decompensated cirrhosis, but its safety has to be confirmed in larger long-term studies with cirrhotic patients.

Our study had some limitations, which should be taken into consideration. First, it was a single-arm, open-label study, without any randomization or control (ideally placebo) arm, which reduce the strength of our findings. Second, the number of study participants was limited and therefore type II errors cannot be excluded. Third, patients with Child-Pugh class C cirrhosis were excluded and thus conclusions about patients with very advanced cirrhosis cannot be drawn. Fourth, the short-term (15-day) empagliflozin administration is insufficient for the evaluation of long-term safety and diuretic efficacy of empagliflozin, although the 6-month follow up under empagliflozin in 27 of 30 patients may provide some insights for long-term data.

In conclusion, this prospective single-arm, open-label study of patients with cirrhosis and T2DM suggests that empagliflozin can increase the 24-h urine volume output and FE_{Na}, without safety issues or adverse effects on electrolyte balance and hemodynamic stability. However, given that it did not significantly increase 24-h urine sodium excretion, the use of empagliflozin in cirrhosis should be evaluated further, preferentially in large randomized controlled trials with long-term follow up. In particular, in patients with compensated cirrhosis, the potential effect of empagliflozin on portal hypertension and the rate of progression to a decompensated state should be assessed. On the other hand, in patients with decompensated cirrhosis, the possible effects of empagliflozin in reducing ascites, edema and the need for ascites paracentesis seem to represent reasonable aims for future studies.

Summary Box

What is already known:

- Empagliflozin, a sodium-glucose cotransporter-2 inhibitor, is a glucose-lowering agent that acts by inducing glucosuria and natriuresis, exhibiting antihyperglycemic, diuretic, and cardio-renal protective effects
- While primarily indicated for the treatment of type 2 diabetes mellitus (T2DM), empagliflozin has also shown benefits in patients with heart failure and chronic kidney disease, due to its extra-glycemic effects
- Data regarding the safety and efficacy of empagliflozin in patients with cirrhosis are limited and mostly derived from large cardiovascular outcome trials in non-cirrhotic populations

What the new findings are:

- In patients with T2DM and cirrhosis, empagliflozin significantly increased diuresis without causing clinically relevant electrolyte imbalances or deterioration in renal function
- A trend toward increased natriuresis was observed, although the difference did not reach statistical significance
- Glycemic control improved over the 6-month treatment period, while renal function remained stable, with only mild and non-progressive changes observed

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