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RESEARCH ARTICLE

Impact of Empagliflozin on Liver Fibrosis in Patients with Type 2 Diabetes and Nonalcoholic Steatohepatitis

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Abstract: ***Background***: Nonalcoholic fatty liver disease (NAFLD) is a prevalent comorbidity in type 2 diabetes mellitus (T2DM) patients, often progressing to nonalcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and hepatocellular carcinoma. Empagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, has shown favorable metabolic and cardiorenal outcomes, but its role in hepatic fibrosis remains underexplored. ***Objective:*** To evaluate the impact of empagliflozin on liver fibrosis and related biochemical parameters in patients with T2DM and NASH. ***Methods:*** A prospective, randomized, open-label study was conducted at BIRDEM General Hospital, Dhaka, from April to October 2022, enrolling 90 adult T2DM patients with magnetic resonance elastography (MRE)-confirmed NASH. Participants were randomized equally into two groups: Group A received empagliflozin (10 mg/day) plus standard antidiabetic medications, while Group B received standard medications alone, for ≥3 months. Outcomes included liver stiffness, liver enzymes, lipid profile, BMI, and glycemic parameters. Statistical analyses were performed using SPSS v24, with $p<0.05$ considered significant. ***Results:*** Both groups were comparable at baseline in terms of demographic and clinical characteristics ($p>0.05$). After 3 months, Group A showed significant reductions in weight (76.91±6.4 vs. 73.52±6.8 kg, $p<0.001$), BMI (22.52±4.6 vs. 21.47±4.6 kg/m², $p<0.001$), FBS, 2HABF, and HbA1c (7.65±1.5 → 7.27±1.47, $p=0.012$). Liver enzymes (AST, ALT, GGT) and lipid parameters (TC, TG, LDL) decreased significantly in the empagliflozin group, whereas the control group showed smaller or non-significant changes. Liver stiffness (3.40±0.40 → 3.28±0.46 kPa, $p=0.031$) and fibrosis staging improved significantly in the empagliflozin group but not in the control group. ***Conclusion:*** Empagliflozin demonstrated significant improvements in glycemic control, weight, BMI, liver enzymes, lipid profile, and liver stiffness in T2DM patients with NASH. These findings suggest empagliflozin may have therapeutic potential in mitigating hepatic fibrosis. Larger trials with biopsy confirmation and longer follow-up are warranted.

Keywords: Empagliflozin, Nonalcoholic Steatohepatitis, Type 2 Diabetes Mellitus, Liver Fibrosis, SGLT2 inhibitors.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease, affecting 17–46% of the population worldwide.[1] NAFLD has a spectrum ranging from fatty liver alone to nonalcoholic steatohepatitis (NASH) to liver fibrosis.[2-3] Approximately 20–30% of patients with NAFLD also have nonalcoholic steatohepatitis (NASH), which can cause liver fibrosis and progresses to cirrhosis with a risk of hepatocellular carcinoma in 10–20% of patients.[4-5] NAFLD also leads to various extrahepatic complications. For instance, NAFLD is an independent risk factor for cardiovascular disease,[6] type 2 diabetes,[7] and chronic kidney disease.[8] Between 50 and 70% of patients with type 2 diabetes mellitus (T2DM) have NAFLD, with as many as 30–40% having nonalcoholic steatohepatitis (NASH).[9,10]Early detection of severe steatosis and significant fibrosis would be useful to identify patients who may have aggressive NAFLD and therefore need further evaluation. Since a high proportion of NAFLD patients are asymptomatic for a long period of time and have normal or only slightly abnormal liver function tests, non-invasive methods for early identification of severe steatosis and advanced fibrosis/cirrhosis are needed[11] to allow early treatment of NAFLD in high-risk patients with type 2 diabetes.

The pathogenesis of NAFLD is complex, involving insulin resistance, oxidative stress, lipid peroxidation, and mitochondrial dysfunction.[12] Insulin resistance is the key pathogenic factor for the development of both type 2 diabetes and NAFLD.[13,14] Several anti-diabetic therapies have been investigated in the treatment of NAFLD with varying results, including lifestyle modification,[15,16] metformin,[17] pioglitazone,[18,19]and liraglutide.[20]

Newer classes of anti-diabetic medications may be useful for the treatment of NASH. Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a new class of oral anti-diabetic drugs that reduce hyperglycemia independently of insulin secretion by promoting the urinary excretion of glucose.21 It inhibits SGLT2 at the proximal renal tubule, responsible for ~ 90% of glucose reabsorption in the kidney. The consequent renal glycosuria lowers blood glucose and also helping in weight loss.22 Furthermore, SGLT2 inhibitors are also shown to reduce waist circumference and systolic and

diastolic blood pressure in T2DM patients.23 Empagliflozin is an SGLT2 inhibitor that has also proved to improve cardiorenal outcomes in T2DM patients.

Specifically, empagliflozin was shown to reduce cardiovascular and all-cause mortality, hospitalization and death from heart failure, new-onset or worsening nephropathy, and a composite renal outcome. Uniquely, these benefits can be observed very early and within three months of empagliflozin initiation.[23–25] Improvement in insulin resistance (hyperinsulinemia) results in the downregulation of Sterol regulatory element-binding protein 1 (SREBP-1c) and the blockage of de novo hepatic lipogenesis.[26] Thus, SGLT-2 inhibitors should improve NAFLD and/or NASH and provide a mechanistic rationale to conduct human trials with SGLT-2 inhibitors in patients with NAFLD.

The conventional standard for diagnosing and staging liver fibrosis is the percutaneous biopsy, which is invasive, expensive, has poor patient acceptance, is prone to inter-observer variability and sampling errors, has poor repeatability, and carries a risk of complications estimated at 3% with a mortality rate of 0.03%.[27–30]

MRE (Magnetic resonance elastography) has a low rate of technical failure compared with transient ultra-sound elastography. MRE is the only non-invasive technique that has been able to stage liver fibrosis or diagnose mild fibrosis with reasonable accuracy, as reported by a recent systemic review of imaging techniques for the diagnosis and staging of hepatic fibrosis.[31] Studies have shown that MRE is highly reproducible in both volunteers and patients with liver fibrosis.[32–34]

MATERIALS AND METHODS

This prospective, randomized, open-label study was conducted at the Department of Gastrointestinal Hepatobiliary and Pancreatic Disorders, BIRDEM General Hospital, Dhaka, from April to October 2022. Adult patients (>18 years) with type 2 diabetes mellitus (T2DM) and MRE-confirmed NASH were enrolled. Patients were randomly assigned (1:1) using computer-generated numbers to either the empagliflozin group (10 mg/day, ≥3 months) or the control group, with investigators performing imaging analyses blinded to allocation. In this study, 45 patients were included in each group. Therefore, total 90 patients were included. Exclusion criteria included significant alcohol intake, other liver diseases, recent use of drugs affecting liver fat, cirrhosis, substance abuse, pregnancy, or elevated liver enzymes >3× upper normal limit. The main outcome was hepatic fibrosis, with secondary outcomes including liver enzymes (ALT/AST), BMI, and HbA1c. Data were collected via face-to-face interviews, clinical examinations, and review of laboratory records, checked for completeness and consistency, and analyzed using SPSS v24. Continuous variables were expressed as mean ± SD, categorical variables as frequency and percentage. Comparisons were made using Student's t-test, paired t-test, chi-square, or Fisher's exact test as appropriate, with $p < 0.05$ considered statistically significant. Ethical approval was obtained from the BIRDEM ethical review committee, and written informed consent was obtained from all participants.

RESULTS

Table 1 shows the Baseline demographic characteristics of study participants. Mean age of group A and B were 49.11±7.90 and 46.98±10.19 year respectively. Most of patients from each group was belonged to 40 – 49 years (37.8% and 40% respectively). Male were predominantly high in each group (77.8% and 84.4% respectively). Most common occupation was service holder (31.1%) in group A, while farmer and fisherman were mostly seen among group B (20% and 17.8% accordingly). There were no statistically significant differences between the two groups in terms of age, gender, or occupational status ($p > 0.05$), indicating that the baseline demographic characteristics were comparable across both groups.

Table-1: Baseline demographic characteristics of study participants (n=90)

Characteristic	Group A (Empagliflozin + other DM drugs, n=45)	Group B (Usual DM medications, n=45)	p-value
Age (years, mean ± SD)	49.11 ± 7.90	46.98 ± 10.19	>0.05**
Age group (years), n (%)			
30–39	8 (17.8%)	14 (31.1%)	
40–49	17 (37.8%)	18 (40.0%)	
50–59	15 (33.3%)	9 (20.0%)	>0.05***
≥60	5 (11.1%)	4 (8.9%)	
Gender, n (%)			
Male	35 (77.8%)	38 (84.4%)	>0.05*
Female	10 (22.2%)	7 (15.6%)	
Occupation, n (%)			
Service holder	14 (31.1%)	12 (26.7%)	
Farmer	8 (17.8%)	9 (20.0%)	
Fisherman	7 (15.6%)	8 (17.8%)	>0.05*
Businessman	4 (8.9%)	6 (13.3%)	

Housewife	5 (11.1%)	6 (13.3%)	
Others	7(15.6%)	4 (8.9%)	

Student's t-test,Fisher's Exact test and *Chi-square test were done*

Baseline weight and BMI was significantly decreased in post-treatment assessment among empagliflozin group participants ($p<0.05$), though, in non-Empagliflozin group only BMI showed significant improvement. Systolic and diastolic blood pressure did not show any statistical improvement in both groups (Table 2).

Table 2: Baseline characteristics of general examination and changes in parameters after 3 months of treatment (n=90)

	Group A n (%)			Group B n (%)			p value**
	Baseline n=45	Post-treatment n=42	p value*	Baseline n=45	Post-treatment n=41	p value*	
Weight (kg)	76.91±6.4	73.52±6.8	<0.001	76.68±7.6	76.39±7.9	0.067	0.081
BMI (kg/m2)	22.52±4.6	21.47±4.6	<0.001	24.27±5.2	23.78±5.1	0.083	0.033
SBP (mmHg)	125.5±7.9	125.4±7.7	0.425	128.28±8.2	126.63±7.3	0.120	0.461
DBP (mmHg)	81.2±12.3	81.0±11.2	0.702	83.73±9.1	83.41±8.1	0.950	0.267

**Paired t test and **student t-test were done.*
Group A: Patients received Empagliflozin with other diabetic drug
Group B: Patients received usual DM medications other than Empagliflozin

Among the participants, 7.8% had chronic kidney disease and 5.6% had ischemic heart disease as past illnesses. All patients had type 2 diabetes mellitus (100%), with dyslipidemia (74.4%) and hypertension (41.1%) being the most common co-morbidities. Multiple co-morbidities were observed in 87.8% of the participants (Table3).

Table 3: Distribution of Past Illnesses and Co-morbidities among participants (n=90)

History of Illness / Co-morbidities	Frequency (n)	Percentage (%)
Past Illnesses*		
Chronic kidney disease	7	7.8
Ischemic heart disease	5	5.6
Co-morbidities*		
Type 2 diabetes mellitus	90	100
Dyslipidemia	67	74.4
Hypertension	37	41.1
Nausea/vomiting	6	6.7
Multiple co-morbidities	79	87.8

**Multiple responses were considered.*

Maximum participants had used anti-diabetic drugs in both empagliflozin and non-Empagliflozin group (80% and 77.8% respectively) in this study and also majority of the participants had oral anti-diabetic drug (51.1% and 64.4% accordingly). In that case, metformin was most common drug of choice (35.6% and 42.2%) in both groups. Insulin was also taken about 22.2% in empagliflozin group and 13.3% in non-Empagliflozin group of participants. Yet, a good amount of participants had history of no medication (26.7% and 22.2%) in both empagliflozin and non-Empagliflozin group respectively (Table 4).

Table-4: History of drug among participants in between two groups (n=90)

History of drug	Group A n=45(%)	Group B n=45(%)	p value*
Anti-diabetic drug	36(80)	35(77.8)	0.796
Type of drug			0.392
Insulin	10(22.2)	6(13.3)	
Oral	23(51.1)	29(64.4)	
No medication	12(26.7)	10(22.2)	
Metformin	16(35.6)	19(42.2)	0.517
Sulfonylurea	8(17.8)	5(11.1)	0.368
DPP4-Inhibitor	8(17.8)	7(15.6)	0.777

*Chi-square test was done.
Group A: Patients received Empagliflozin with other diabetic drugs
Group B: Patients received usual DM medications other than Empagliflozin

Table 5 summarizes alterations in glycemic control, hepatic enzymes, lipid levels, and liver stiffness following 3 months of treatment in both groups. Empagliflozin significantly improved glycemic control (FBS, 2HABF, HbA1c), reduced liver

enzymes (AST, ALT, GGT), and improved lipid profile (TC, TG, LDL) after 3 months. Liver stiffness (kPa) also decreased significantly in the empagliflozin group, with a shift toward milder fibrosis stages. In contrast, the control group (usual DM medications) showed smaller or non-significant improvements, except for some lipid reductions. Between-group analysis showed empagliflozin's effects were particularly notable for GGT and liver stiffness stage improvements.

Table 5: Changes in Glycemic Status, Liver Enzymes, Lipid Profile, and Liver Stiffness after 3 Months of Treatment between Groups (n=90)

Parameter	Group A (Empagliflozin + other DM drugs)	p value (within-group*)	Group B (Usual DM medications)	p value (within-group*)	p value (between-group**)
Glycemic Status					
FBS (mmol/L)	7.18 ± 0.68 → 6.8 ± 0.41	<0.001	7.61 ± 0.99 → 6.89 ± 0.58	<0.001	0.403
2HABF (mmol/L)	7.5 ± 0.66 → 7.3 ± 0.69	0.001	7.68 ± 0.84 → 7.59 ± 0.89	0.022	0.110
HbA1c (%)	7.65 ± 1.5 → 7.27 ± 1.47	0.012	7.35 ± 1.2 → 7.42 ± 1.34	0.487	0.624
Liver Enzymes & Biochemical Profile					
AST (IU/L)	43.25 ± 3.8 → 41.17 ± 4.1	<0.001	42.9 ± 4.4 → 42.32 ± 3.6	0.402	0.184
ALT (IU/L)	56.04 ± 7.7 → 52.53 ± 7.5	<0.001	55.35 ± 6.5 → 53.72 ± 8.6	0.098	0.501
GGT (IU/L)	67.4 ± 4.4 → 59.77 ± 5.1	<0.001	69.42 ± 4.5 → 68.0 ± 6.8	0.090	<0.001
ALP (IU/L)	87.4 ± 19.5 → 85.3 ± 16.9	0.285	88.53 ± 19.4 → 87.14 ± 19.6	0.335	0.643
Serum Creatinine (mg/dl)	0.88 ± 0.09 → 0.90 ± 0.12	0.111	0.87 ± 0.09 → 0.86 ± 0.11	0.155	0.135
Serum Albumin (gm/L)	4.38 ± 0.57 → 4.39 ± 0.50	0.979	4.42 ± 0.63 → 4.3 ± 0.68	0.168	0.459
Lipid Profile					
Total Cholesterol (mg/dl)	177.4 ± 19.7 → 170.9 ± 18.1	<0.001	177.6 ± 18.1 → 168.7 ± 16.5	0.022	0.554
Triglycerides (mg/dl)	138.4 ± 15.1 → 132.8 ± 14.2	<0.001	145.5 ± 16.1 → 139.0 ± 20.3	0.025	0.111
LDL (mg/dl)	109.6 ± 16.7 → 103.7 ± 17.1	<0.001	109.7 ± 18.8 → 104.8 ± 17.3	0.014	0.764
HDL (mg/dl)	46.8 ± 13.4 → 48.9 ± 13.5	0.217	44.36 ± 13.1 → 45.8 ± 11.4	0.104	0.272
Liver Stiffness (LS)					
LS (kPa, mean ± SD)	3.40 ± 0.40 → 3.28 ± 0.46	0.031	3.42 ± 0.40 → 3.35 ± 0.44	0.088	0.624
Stages of LS (n, %)					
Normal / Inflammation	2 (4.4) → 8 (17.8)	0.007***	4 (8.9) → 4 (8.9)	0.135***	0.177#
Stage 1–2 fibrosis	24 (53.3) → 21 (46.7)		21 (46.7) → 29 (64.4)		
Stage 2–3 fibrosis	16 (35.6) → 12 (26.7)		18 (40) → 6 (13.3)		
Stage 3–4 fibrosis	3 (6.7) → 1 (2.2)		2 (4.4) → 2 (4.4)		

** Paired t-test (within-group), ** Student's t-test (between groups). *** McNemar test., # Chi-square test.*

DISCUSSION

According to this study, no significant differences were found between the two groups of patients regarding, both mean age and age group distribution, gender and occupational status (p value >0.05). Mean age of empagliflozin group and non-Empagliflozin were 49.11±7.90 and 46.98±10.19 year respectively. Highest percentage of patients from each group was belonged to 40 – 49 years (37.8% and 40% respectively). Male were predominantly high in each group (77.8% and 84.4% respectively) and as occupation most common was service holder (31.1%) in empagliflozin group , while farmer and fisherman were mostly seen among and non-Empagliflozin group (20% and 17.8% accordingly). In a similar study of NAFLD with T2DM patients, 68 (81%) were males and the majority of the patients belonged to the age group of 41-50 years (42.86%), with mean age of the patients was 47.23 ± 10 years.[35]

Baseline weight (76.91±6.4 vs. 73.52±6.8 kg) and BMI (22.52±4.6 vs. 21.47±4.6 kg/m2) was significantly decreased in post-treatment assessment among empagliflozin group participants ($p<0.05$), though, non-Empagliflozin group did not show any statistically significant improvement. Systolic and diastolic blood pressure had no significant improvement with baseline and post-treatment assessment and also in between groups. In the empagliflozin group, weight and BMI decreased significantly ($p<0.001$ for both).[36] According to Zhang et al., meta-analysis, compared with the control group, empagliflozin in comparison to control group could significantly reduce the body mass index (BMI) (MD: −0.98 [95% CI: −1.87, −0.10], p = 0.03) among participants.[37]

More recently, empagliflozin was proven superior in Comparison to control group for reduction of major adverse cardiovascular risk among patients with T2DM and established CVD.[38] However, in this study, only a few participants presented with chronic kidney disease (7.8%) and ischemic heart disease (5.6%). All participants had type 2 diabetes mellitus (100%), along with dyslipidemia (74.4%), hypertension (41.1%). Multiple co-morbidities were found among 87.8% of participants.

Maximum participants used anti-diabetic drugs in both empagliflozin and non-Empagliflozin group (80% and 77.8% respectively) in this study and also majority of the participants taking oral anti-diabetic drug (51.1% and 64.4% accordingly). In that case, metformin was most common drug of choice (35.6% and 42.2%) in both groups. Insulin was also taken about 22.2% in empagliflozin group and 13.3% in non-Empagliflozin group of participants. Yet, a good number of participants had history of no medication (26.7% and 22.2%) in both empagliflozin and non-Empagliflozin group respectively. SGLT2is are considered the most effective therapies for lipid modulation in these patients.[39] Also metformin was most common medication, along with insulin and DPP4-inhibitor were found in Bañares et al.[40]

In this study, majority of the participants were non-smoker in both groups, however, about 17.8% were smoker in empagliflozin group and 13.3% were smoker in non-Empagliflozin group of participants. However, smoking history were found two times more in NAFLD patients (OR, 2.0; 95% CI, 1.4-3.0) in Hsing et al.[41]

Mean value of fasting blood sugar and 2 hours after breakfast was significantly lower over post-treatment assessment compared with baseline in both groups. Also, HbA1C was significantly decreased in post-treatment in empagliflozin group than baseline. The mean HbA1c values, pre- and post-treatment, were 8.19 ± 0.93% and 7.50 ± 0.89% respectively, and the mean reduction was 0.69%, which was statistically significant, also the mean FBS was 9.28 ± 2.68 mg/dL and 7.46 ± 2.76 mmol/L at baseline and post-treatment respectively.[35]

Liver enzymes were significantly decreased post-treatment compared to baseline assessment in empagliflozin group participants, while non-Empagliflozin group did not differ post-treatment values. The two groups showed a significant difference for change in serum ALT level (P = 0.005) and nonsignificant differences for AST (P = 0.212) and GGT (P = 0.057) levels.[42] Also post-treatment serum creatinine was significantly increased in empagliflozin group. Serum Albumin level had no significant association post-treatment assessment in both groups. Mean total cholesterol, triglyceride and low-density lipoprotein were significantly lowered in post-treatment assessment in both groups. There was a significant improvement of the lipid profile (TG, total cholesterol, LDL-C, VLDL-C, TC to HDL-C ratio, TG to HDL-C and LDL to HDL-C ratio) in the patients who are administrated SGLT2 inhibitors in comparison to the control group (p value <0.05) discussed in a alike study of Gameil et al.[43]

Magnetic resonance elastography (MRE), a non-invasive technique, was done in this study, to evaluate liver stiffness and stages of liver fibrosis. post-treatment mean of liver stiffness was significantly decreased compared to baseline status in empagliflozin group (3.28±0.46 vs. 3.40±0.40 kPa), though, non-Empagliflozin group did not show any significantly improvement in post-treatment assessment. Stages of liver stiffness showed, on baseline assessment maximum participants were in stage 1 to 2 fibrosis (53.3%) in both Empagliflozin group and (46.7%) in non-Empagliflozin group. Nevertheless, after treatment, stages of liver stiffness show significant improvement with baseline findings in empagliflozin group, but not for non-Empagliflozin group. After treatment though most of the participants were in stage 1 to 2 fibrosis (46.7%), along with other stages participants were lower than baseline. This findings were similar to another study, as LSM was significantly decreased after 24 weeks in the empagliflozin group (6.03 ± 1.40 kPa to 5.33 ± 1.08 kPa, P = 0.001), while the slight decrease in the non-Empagliflozin group was not significant (5.56 ± 1.05 kPa to 5.35 ± 0.96 kPa, P = 0.139).[44] With above all findings, it was clear that empagliflozin had a good response in case of liver fibrosis and other bio-chemical profile also improved post-treatment in empagliflozin group of participants. Bottom of Form

CONCLUSION

In the current study, we explored and investigated the effects of empagliflozin on hepatic fibrosis in type 2 diabetes mellitus patients and found that empagliflozin had a significant impact on NAFLD patients. post-treatment assessment of participants show significant changes in weight, BMI, HbA1C, total cholesterol, triglyceride, low density lipoprotein, AST, ALT and GCT, along with other bio-chemical parameters. Also, a

significant improvement had been noticed in liver stiffness and stages of liver fibrosis by MRE. Though in Empagliflozin group we observed there is reduction in of certain parameter than baseline but there is no significant difference seen between Empagliflozin and control group in post-treatment assessment. However, further study with liver biopsy and long-term follow-up is warranted.

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