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EDITORIAL

Cheng CH, Hao WR, Cheng TH. Harnessing aryl hydrocarbon receptor dynamics: Unveiling therapeutic pathways in esophageal squamous cell carcinoma. *World J Exp Med* 2024; 14(4): 98599 [DOI: [10.5493/wjem.v14.i4.98599](https://doi.org/10.5493/wjem.v14.i4.98599)]

REVIEW

Wibowo DP, Agustiningsih A, Jayanti S, Sukowati CHC, El Khobar KE. Exploring the impact of hepatitis B immunoglobulin and antiviral interventions to reduce vertical transmission of hepatitis B virus. *World J Exp Med* 2024; 14(4): 95960 [DOI: [10.5493/wjem.v14.i4.95960](https://doi.org/10.5493/wjem.v14.i4.95960)]

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ORIGINAL ARTICLE**Retrospective Study**

Salzillo C, Basile R, Cazzato G, Ingravallo G, Marzullo A. Value of autopsy in the modern age: Discrepancy between clinical and autopsy diagnoses. *World J Exp Med* 2024; 14(4): 95147 [DOI: [10.5493/wjem.v14.i4.95147](https://doi.org/10.5493/wjem.v14.i4.95147)]

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Clinical Trials Study

Seif El-Din Z, Afify M, Zayed E, Elsabaawy D, Tharwa ES, Elsharawy A, Abdelsameea E, Rady MA. Dapagliflozin as an oral antihyperglycemic agent in the management of diabetes mellitus in patients with liver cirrhosis. *World J Exp Med* 2024; 14(4): 95272 [DOI: [10.5493/wjem.v14.i4.95272](https://doi.org/10.5493/wjem.v14.i4.95272)]

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Clinical Trials Study

Dapagliflozin as an oral antihyperglycemic agent in the management of diabetes mellitus in patients with liver cirrhosis

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Abstract

BACKGROUND

The use of dapagliflozin in patients with cirrhosis has been relatively restricted due to concerns regarding its overall safety and pharmacological profile in this population.

AIM

To determine the safety and effectiveness of dapagliflozin in the co-management of diabetes mellitus and cirrhosis with or without ascites.

METHODS

The patients studied were divided into two groups: 100 patients in the control group received insulin, while 200 patients received dapagliflozin. These patients were classified as Child A, B, or C based on the Child-Pugh classification. Child A or B and Child C were administered doses of 10 mg and 5 mg of dapagliflozin, respectively.

RESULTS

The rate of increased diuretics dose was markedly elevated in the group that received insulin compared to the group that received dapagliflozin. In addition, dapagliflozin treatment substantially reduced weight, body mass index, and fasting blood glucose compared to the insulin group during follow-up. However,

there were no significant differences in hemoglobin A1c, liver function, or laboratory investigations between both groups during the follow-up period. The incidence of hypoglycemia, hepatic encephalopathy, variceal bleeding, and urinary tract infection was significantly higher in the insulin group compared to the dapagliflozin group. In contrast, the dapagliflozin group experienced significantly higher rates of frequent urination and dizziness. In addition, the insulin group exhibited a marked worsening of ascites compared to the dapagliflozin group.

CONCLUSION

Dapagliflozin demonstrated safety and efficacy in the treatment of diabetic patients who have cirrhosis with or without ascites. This resulted in an improvement of ascites, as well as a decrease in diuretic dose and Child–Pugh score.

Key Words: Dapagliflozin; Cirrhosis; Diabetes mellitus; Hemoglobin; Liver diseases

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Core Tip: To assess the effectiveness and safety of dapagliflozin in the co-management diabetes mellitus and cirrhosis with or without ascites, patients were categorized into a control group of 100 patients administered insulin and 200 patients administered dapagliflozin. On follow-up, there was a significantly higher incidence of hypoglycemia, hepatic encephalopathy, variceal bleeding, and urinary tract infection in the insulin group than in the dapagliflozin group. Frequent micturition and vertigo were significantly higher in the dapagliflozin group. Dapagliflozin demonstrated safety and efficacy in the treatment of diabetic patients with cirrhosis, leading to improvement of ascites, decrease in diuretic dose, and Child–Pugh score.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder closely associated with the onset and progression of chronic liver diseases (CLD). It is characterized by changes in insulin sensitivity and impaired blood glucose regulation[1]. The number of patients affected by DM is expected to increase, with a prevalence of 22%-40% in cirrhotic cases[2]. In addition to serving as the primary site for insulin clearance, the liver plays a substantial role in maintaining blood glucose homeostasis.

Liver cirrhosis (LC) is diabetogenic, and diabetes is one of the risk factors for LC. DM leads to an increase in complications and mortality among patients with cirrhosis. Treatment of DM can be challenging in cases of liver failure[3]. Selecting antidiabetic drugs for patients with both CLD and DM is complex due to the potential impact of liver damage on the metabolism of diabetes medications.

The long-term effects of antidiabetic medications have received significant interest in patients with CLD[4]. These patients experience different severe comorbidities such as lactic acidosis, hypoglycemia, malnutrition, impaired renal function, and hypoalbuminemia. The pharmacokinetics of most antidiabetic drugs, except for insulin, necessitate dose titration. There are concerns regarding the management of diabetes in CLD cases, particularly those that involve the use of novel antidiabetic agents. To our knowledge, there are no explicit guidelines pertaining to this issue[5].

The mechanism of action of sodium-glucose cotransporter-2 (SGLT2) inhibitors as antidiabetic agents involves the inhibition of glucose reabsorption in the proximal renal tubule, which leads to a decrease in serum levels and a loss of glucose in urine. SGLT2 is a significant enzyme in the kidney that is responsible for the reabsorption of glucose. Inhibiting this enzyme lowers the threshold for glucose excretion in urine. Increased glucose loss results in calorie loss, a decrease in serum glucose levels, and mild osmotic diuresis. Additionally, SGLT2 inhibitors induce a slight decrease in blood pressure (BP) and moderate weight loss, contributing to their beneficial effects. Empagliflozin, dapagliflozin, and canagliflozin, which are SGLT2 inhibitors, reduce cardiovascular complications and mortality in individuals with type 2 diabetes (T2D) and cardiovascular issues. In cases of chronic kidney disease and T2D, they also reduce the risk of hospitalization for heart failure and end-stage renal disease[6]. In high-risk individuals with T2D, long-term therapy is advised to mitigate cardiovascular events, end-stage renal failure, renal disease progression, and hospitalization and mortality due to heart failure. Administering dapagliflozin early in acute heart failure hospitalization is both safe and contributes to one aspect of optimization[7], and dapagliflozin does not disrupt liver function tests. The observed decrease in aspartate aminotransferase (AST) levels and lack of impact on other liver function parameters indicate that dapagliflozin may be used as an adjunctive treatment to metformin in diabetic liver diseases[8].

Dapagliflozin is available in 10 mg and 5 mg tablets under the brand name Forxiga. The recommended dosage is 5-10 mg, once daily. SGLT2 inhibitors commonly have adverse effects, including genital mycotic infections, increased thirst, and urinary tract infections (UTIs). Less frequently reported side effects include ketoacidosis, hypersensitivity reactions, hypoglycemia, hypovolemia, dehydration, and elevated levels of creatinine and serum cholesterol. Dapagliflozin is associated with an increased risk of necrotizing fasciitis of the perineum in T2D patients[9].

MATERIALS AND METHODS

This study was performed at the Gastroenterology and Hepatology Unit, National Liver Institute Hospital, Menoufia University, Egypt, from November 2020 to November 2022. Following the institutional review board's approval (IRB number: 00248/2021), all patients who participated provided written informed consent. This prospective study was conducted on patients with cirrhosis and DM (with or without ascites) to determine the safety and efficacy of dapagliflozin in the co-management of DM and cirrhosis.

The patients were divided into 100 patients as controls who received insulin as a treatment for diabetes, those classified as Child A, B, or C based on the Child–Pugh classification[10], and 200 patients administered dapagliflozin as a treatment for diabetes. Participants classified as Child A or B received a daily 10 mg dose of dapagliflozin, while Child C patients received a daily 5 mg dose of dapagliflozin. All patients were adults over the age of 18 who had been diagnosed with cirrhosis and diabetes based on the criteria set by the American Diabetes Association, including random plasma glucose \geq 200 mg/dL, oral glucose tolerance test \geq 200 mg/dL, 2-h plasma glucose (during 75 g), fasting plasma glucose \geq 126 mg/dL, and a hemoglobin A1c (HbA1c) \geq 6.5% [11].

We excluded patients under the age of 18, diabetic patients receiving combination therapy, and patients with hepatic dysfunction along with renal impairment. Age, sex, duration of diabetes, changes in insulin doses, changes in diuretic doses, and the presence of comorbidities such as hypertension, coronary heart disease, and dyslipidemia were collected during baseline and at 12-week assessments of all patients. All groups were matched in terms of age and sex. The duration of insulin use was established, and we evaluated weight loss, alterations in body mass index (BMI), and changes in BP. Furthermore, modifications in HbA1c, fasting glucose level, lipid profile, estimated glomerular filtration rate (eGFR) value, serum potassium, uric acid level, gamma-glutamyl transferase, alanine aminotransferase (ALT with normal range 10-44 IU/L), AST with normal range 10-34 IU/L, serum sodium, and modifications in abdominal ultrasound findings were evaluated. The documented side effects of the treatment included UTI, proteinuria, frequent micturition, vertigo, hepatic encephalopathy, variceal bleeding, hepatocellular carcinoma, pyelonephritis, hypoglycemia, genital infection, syncope, hypotension, dehydration, abdominal discomfort, back pain, dizziness, rash, and phlebitis.

Statistical analysis

Data was collected and entered into the computer utilizing the 22nd version of SPSS software (IBM Corp., Armonk, NY, United States). Descriptive statistics were expressed as mean \pm standard deviation (SD) and range (for quantitative data). The χ^2 test was utilized to assess the association between qualitative variables. In addition, the student *t*-test was utilized to compare the SD and mean of two data sets with normal distribution. In contrast, the Whitney test was used for data with non-normal distribution. Additionally, Pearson's correlation was utilized to examine the correlation between two normally distributed variables, while Spearman's correlation was utilized in non-normally distributed variables. The Fisher exact test was utilized for 2 \times 2 qualitative variables when $>$ 25% of the cells have an expected count of $<$ 5. A *P*-value $<$ 0.05 was considered statistically significant.

RESULTS

There were no significant differences between patients receiving dapagliflozin treatment and controls in terms of age, sex, duration of illness, smoking, contact with canal water, and associated comorbidities ($P >$ 0.05). **Table 1** summarizes clinical data among the study groups. The dapagliflozin group comprised 56 patients classified as Child A, 81 as Child B, and 63 as Child C, with percentages of 28%, 40.5%, and 31.5%, respectively. The insulin group included 24 patients in Child A, 32 in Child B, and 44 in Child C, with percentages of 24%, 32%, and 44%, respectively. Of the patients in the dapagliflozin group, 151 had positive hepatitis C virus (HCV). In contrast, the group receiving insulin consisted of 78 HCV patients. Direct-acting antivirals (DAAs) were administered to 146 patients in the dapagliflozin group who tested positive for HCV, while interferon therapy was administered to five patients. DAAs were administered to 76 patients in the insulin group, and two patients underwent interferon therapy. The diuretic dosage did not change in any of the 150 patients in the dapagliflozin group. However, 50 patients in this group did increase their diuretic dose. The insulin group did not experience any changes in their diuretic dose. A total of 18 patients maintained their diuretic dose, while 12 patients experienced a reduction in their dose. Additionally, diuretic medication was ceased in eight patients, while the dosage increased in 41 patients. The result was highly statistically significant ($P <$ 0.0001) (**Figure 1**).

The results displayed in **Table 2** show a significant decrease in weight, BMI, fasting blood glucose, HbA1c, and serum K following the administration of dapagliflozin ($P <$ 0.05). Prior to dapagliflozin, the AST level was 49, which decreased to 44 after treatment. Similarly, the ALT level remained at 30 both before and after dapagliflozin treatment. Therefore, no substantial difference was observed in liver enzymes.

Table 1 Comparison of demographic data among the study groups

Parameter	Dapagliflozin group, n = 200	Insulin group, n = 100	Test of sig.	
			t/ χ^2	P value
Age in years				
mean \pm SD	56.84 \pm 7.48	56.96 \pm 9.29	0.121	0.904
Range	42-76	33-80		
Sex				
Male	96 (48)	44 (44)	0.258	0.611
Female	104 (52)	56 (56)		
Smoking				
Yes	59 (29.5)	38 (38)	2.202	0.137
No	141 (70.5)	62 (62)		
Contact with canal water				
Yes	119 (59.5)	59 (59)	0.007	0.933
No	81 (40.5)	41 (41)		
Comorbidities ¹				
Cardiac ischemia	16 (8)	11 (11)	0.733	0.392
HTN	32 (16)	21 (21)	1.146	0.284
Dyslipidemia	16 (8)	11 (11)	0.733	0.392
None	160 (80)	73 (73)	1.883	0.170
Child classification				
A	56 (28)	24 (24)	4.599	0.100
B	81 (40.5)	32 (32)		
C	63 (31.5)	44 (44)		
Causes of cirrhosis				
Unknown	33 (16.5)	14 (14)	0.321	0.956
HBV	2 (1)	1 (1)		
HCV	151 (75.5)	78 (78)		
Bilharziasis	14 (7)	7 (7)		
Treatment of HCV Infection				
No	49 (24.5)	22 (22)	0.329	0.849
Interferon	5 (2.5)	2 (2)		
DAAAs	146 (73)	76 (76)		
Diuretic dose change				
No change	150 (75)	18 (18)	55.162	< 0.0001 ¹
Decreased dose	0 (0)	12 (12)		
Stopped	0 (0)	8 (8)		
Increased	50 (25)	41 (41)		

¹Some patients have more than 1 comorbidity.

Data are n (%) unless otherwise indicated. DAAs: Direct-acting antivirals; HCV: Hepatitis C virus; HTN: Hypertension; SD: Standard deviation.

Table 2 Comparison of body mass index, blood pressure and laboratory investigations before and after dapagliflozin treatment

Parameter	Dapagliflozin before, n = 200		Dapagliflozin after, n = 200		Test of sig.	
	Mean	SD	Mean	SD	t	P value
Body weight in kg	90.58	17.14	83.18	13.22	4.836	0.0001
BMI in kg/m ²	31.74	5.24	29.20	4.41	5.251	0.0001
SBP in mmHg	110.18	12.01	109.48	11.62	0.592	0.554
DBP in mmHg	72.30	8.92	71.58	8.66	0.825	0.410
HbA1c as %	9.64	1.74	6.88	1.12	18.906	0.0001
Fasting blood sugar in mg/dL	225.83	92.09	142.98	55.16	10.916	0.0001
Triglycerides in mg/dL	180.46	82.07	167.40	66.19	1.752	0.081
Cholesterol in mg/dL	205.36	58.85	199.02	56.94	1.096	0.274
Creatinine in mg/dL	0.87	0.35	0.86	0.44	0.176	0.860
MELD	11.07	5.09	10.88	5.17	0.37	0.711
MELD-Na	14.40	6.82	14.31	7.06	0.13	0.897
eGFR value in mL/min/1.73 m ²	125.93	59.37	116.12	49.50	1.788	0.075
Uric acid in mg/dL	5.07	1.05	4.89	0.85	1.908	0.057
AST in IU/L	49.06	68.16	44.36	61.00	0.727	0.467
ALT in IU/L	30.74	23.73	30.69	24.57	0.021	0.983
GGT in IU/L	78.64	126.52	77.84	185.29	0.05	0.960
Serum Na in mmol/L	133.48	4.77	133.05	5.64	0.832	0.406
Serum K in mg/dL	4.22	0.50	4.10	0.37	2.554	0.011

ALT: Alanine transaminase; AST: Aspartate aminotransferase; BMI: Body mass index; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; GGT: gamma-glutamyl transferase; HbA1c: Hemoglobin A1c; K: Potassium; MELD: Model for end-stage liver disease; MELD-Na: Model for end-stage liver disease-sodium; NA: Sodium; SBP: Systolic blood pressure.

Table 3 shows a marked decline in weight, BMI, fasting blood glucose, HbA1c, and eGFR on follow-up after 3 months in controls treated with insulin ($P < 0.05$). Furthermore, there was a statistically significant decline in weight, BMI, and fasting blood glucose on follow-up of the dapagliflozin treatment compared to the insulin group (controls) ($P < 0.05$). Conversely, no substantial differences were observed in HbA1c, liver function, laboratory investigations in the insulin (control) group follow-up, and dapagliflozin-treated patients, as shown in **Table 4**.

As depicted in **Table 5**, insulin levels in the control group had markedly elevated hypoglycemia, variceal bleeding, hepatic encephalopathy, and UTIs compared to the dapagliflozin-treated group. Moreover, the dapagliflozin-treated group exhibited higher levels of frequent urination and vertigo.

Follow-up abdominal ultrasonography revealed that 94 patients in the dapagliflozin group had improved ascites, while 106 patients remained stationary. In the insulin group, 30 patients had improved ascites, 34 were stationary, and 36 had worse ascites. Ascites deteriorated significantly more in the insulin (control group) group than in the dapagliflozin-treated group. While the classification of the Child did not change before or after treatment with dapagliflozin, the Child scores decreased from 7.53 to 7.09, with $P = 0.0001$. There was a significant decrease in Child scores following dapagliflozin treatment compared to before dapagliflozin treatment ($P < 0.05$), with non-significant differences ($P > 0.05$).

The Child score increased from 8.68 to 8.74, while the Child classification did not change before and after insulin treatment. In addition, there were no significant differences in Child scores before or after insulin treatment ($P > 0.05$).

DISCUSSION

All patients were matched in sex, age, duration of illness and smoking, contact with canal water, Child classification, causes of cirrhosis, treatment of HCV infection, hypertension, dyslipidemia, and cardiac ischemia. Consequently, no other factors affected the scope of our results. A total of 300 patients were enrolled, 140 of whom were males (46.66%), with a median age of 57 years.

The study demonstrated that the overall dapagliflozin safety profile was comparable (for females and males). Similarly, O'Donoghue *et al* [12] reported no signs of modification regarding dapagliflozin impact in terms of sex. Overall,

Table 3 Comparison of clinical and laboratory investigations at baseline and 3 months later in control group

Parameter	Baseline, n = 100		3 months later, n = 100		Test of sig.	
	Mean	SD	Mean	SD	t	P value
Body weight in kg	95.86	19.13	84.60	14.21	4.725	0.0001
BMI in kg/m ²	33.45	6.08	29.54	5.29	4.86	0.0001
SBP in mmHg	112.00	15.04	111.20	12.97	0.403	0.688
DBP in mmHg	70.80	10.22	70.80	9.18	0.0001	0.999
HbA1c as %	10.22	2.03	7.47	1.11	11.9	0.0001
Fasting blood sugar in mg/dL	299.26	77.57	174.74	63.29	12.438	0.0001
Triglycerides in mg/dL	240.04	78.18	221.62	51.48	1.968	0.050
Cholesterol in mg/dL	230.20	77.26	223.64	79.44	0.592	0.555
Creatinine in mg/dL	0.98	0.44	0.99	0.57	-0.144	0.886
MELD	12.46	5.11	12.32	5.60	0.185	0.854
MELD-Na	17.46	6.72	16.70	7.08	0.778	0.437
eGFR value in mL/min/1.73 m ²	119.29	68.19	101.53	46.25	2.141	0.034
Uric acid in mg/dL	4.96	0.80	4.96	0.80	0.0001	0.999
AST in IU/L	74.56	90.09	67.58	81.21	0.575	0.566
ALT in IU/L	40.40	30.79	41.72	31.73	-0.299	0.766
GGT in IU/L	131.98	199.44	131.31	269.69	0.02	0.984
Serum Na in mmol/L	131.42	5.81	131.36	6.78	0.067	0.946
Serum K in mg/dL	4.33	0.62	4.19	0.45	1.857	0.065

ALT: Alanine transaminase; AST: Aspartate aminotransferase; BMI: Body mass index; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; GGT: gamma-glutamyl transferase; HbA1c: Hemoglobin A1c; K: Potassium; MELD: Model for end-stage liver disease; MELD-Na: Model for end-stage liver disease-sodium; NA: Sodium; SBP: Systolic blood pressure.

the dapagliflozin safety profile was comparable for females and males[12]. In this study, we found that the dapagliflozin group had a mean BMI of 31.74 kg/m² prior to treatment and a mean BMI of 29.20 kg/m² following dapagliflozin treatment ($P = 0.0001$). According to our study, the administration of dapagliflozin reduced systolic blood pressure (SBP) from 110.2 to 109.5 mmHg, while diastolic blood pressure (DBP) remained unchanged ($P = 0.554$).

Hassoun *et al*[13] investigated the impact of sex, age, and BMI on secondary outcomes. Their results revealed that sex substantially impacted systolic BP change, as evidenced by patient pulse ($P = 0.048$) and time ($P = 0.047$). In contrast, patients aged > 50 experienced considerably less eGFR change than patients < 50 ($P = 0.012$). Furthermore, the baseline BMI did not show any substantial associations with alterations in secondary outcomes[13]. Hao *et al*[14] illustrated that the reduction in BP associated with dapagliflozin use is attributable to intravascular volume depletion due to its natriuretic and diuretic activities. Nevertheless, studies demonstrated that direct vasodilators have impacted the modulation of the sympathetic nervous system renin-angiotensin-aldosterone system, the efferent arteriole, and increased urinary excretion of uric acid. Notably, the decline in BP is not correlated with the estimated glomerular filtration rate[14]. An examination of 13 clinical trials involving a total of 2360 patients diagnosed with T2D who received a daily dose of dapagliflozin at 10 mg and 2295 patients with T2D who received a placebo revealed that the most significant decrease in BP was observed in patients with pre-existing hypertension at the beginning of the trials. For baseline hypertensive patients (SBP ≥ 140 mmHg), the average decline in DBP and SBP from the starting point to week 24 was -1.2 mmHg and -3.6 mmHg, respectively, after accounting for the placebo effect.

In non-hypertensive patients, the decline in DBP and SBP was -1.2 mmHg and -2.6 mmHg, respectively[15]. Montalvo-Gordon *et al*[16] found that SGLT2 inhibitors can reduce the renin-angiotensin-aldosterone system overactivation by inhibiting sodium and glucose reabsorption in the proximal convoluted tubule. This contributes to restoring the sympathetic nervous system and tubuloglomerular feedback and promotes natriuresis. These effects address the primary mechanisms involved in the development of portal hypertension in cirrhotic patients. Unlike angiotensin-converting enzyme inhibitors, spironolactone, SGLT2 inhibitors, and angiotensin receptor blockers are less effective in lowering overall BP and may be better tolerated by individuals with clinically significant portal hypertension[16]. Heerspink *et al* [17] demonstrated that SGLT2 inhibitors effectively reduce high blood sugar levels and BP by relatively hindering SGLT2 receptors in the kidney's proximal convoluted tubules. This inhibition prevents the reabsorption of filtered glucose and

Table 4 Comparison of clinical and laboratory investigations changes on follow-up in both groups

Parameter	Dapagliflozin, n = 200		Control group, n = 100		Test of sig.	
	Mean	SD	Mean	SD	t	P value
Body weight in kg	11.26	12.12	7.40	21.56	-1.982	0.048
BMI in kg/m ²	3.92	4.35	2.54	6.91	-2.103	0.036
SBP in mmHg	0.70	16.77	0.80	15.68	-0.051	0.959
DBP in mmHg	0.73	11.81	0.00	12.55	0.481	0.631
HbA1c as %	2.77	2.03	2.75	1.67	0.072	0.943
Fasting blood sugar in mg/dL	124.52	66.17	82.86	104.24	-4.206	0.000
Triglycerides in mg/dL	13.06	95.16	18.42	54.61	-0.619	0.537
Cholesterol in mg/dL	6.35	74.66	6.56	41.71	-0.032	0.975
Creatinine in mg/dL	0.01	0.55	-0.01	0.32	0.345	0.730
MELD	0.19	5.76	0.14	3.20	0.097	0.923
MELD-Na	0.09	8.48	0.76	3.09	-0.993	0.321
eGFR value in mL/min/1.73 m ²	10.96	63.42	19.79	57.57	-1.21	0.228
Uric acid in mg/dL	0.18	1.02	0.00	1.14	1.349	0.179
AST in IU/L	4.71	89.72	6.98	37.89	-0.308	0.758
ALT in IU/L	0.05	32.30	-1.32	23.08	0.422	0.673
GGT in IU/L	0.79	218.46	0.67	167.59	0.005	0.996
Serum Na in mmol/L	0.44	7.50	0.06	4.03	0.563	0.574
Serum K in mg/dL	0.11	0.63	0.14	0.61	-0.379	0.705

ALT: Alanine transaminase; AST: Aspartate aminotransferase; BMI: Body mass index; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; GGT: gamma-glutamyl transferase; HbA1c: Hemoglobin A1c; K: Potassium; MELD: Model for end-stage liver disease; MELD-Na: Model for end-stage liver disease-sodium; NA: Sodium; SBP: Systolic blood pressure.

sodium, leading to the excretion of glucose and sodium in the urine. SGLT2 inhibitors reduce preload and afterload, induce volume contraction, and decrease BP (by 1 to 2 mmHg) through the physiological effects of osmotic diuresis and natriuresis, resulting in cardiorenal protection[17]. This study demonstrated a marked elevation in diuretic dosage among individuals treated with insulin compared to those who received dapagliflozin. This can be attributed to the diuretic properties of dapagliflozin treatment. Our results indicated that 75% of patients treated with dapagliflozin did not require any change in their diuretic dose. However, 25% of patients who received dapagliflozin did require an increase in their diuretic dose. Furthermore, a statistically significant finding revealed that 41% of patients undergoing insulin therapy required an increase in their diuretic dosage ($P < 0.0001$). Charaya *et al*[18] demonstrated that the dapagliflozin group had a lower likelihood of increasing the dosage of loop diuretics (14% vs. 30%; $P = 0.048$), lower loop diuretic average doses (78.46 ± 38.95 mg/day vs. 102.82 ± 31.26 mg/day; $P = 0.001$) and more substantial weight loss [4100 (2950; 5750) g vs. 3000 (1380; 4650) g; $P = 0.02$]. The administration of dapagliflozin was associated with a more significant reduction in body weight and reduced requirement for increased diuretic treatment without severe renal function deterioration[19].

Furthermore, we observed a significant decrease in serum K, HbA1c, fasting blood glucose, weight, and BMI levels following dapagliflozin treatment. Dapagliflozin decreases body weight by excretion of glucose in urine and loss of fluids. A significant proportion of the weight loss reported in a composition study, approximately two-thirds, can be ascribed to the reduction in fat mass[19]. In our research, hypoglycemia risk was substantially reduced with dapagliflozin compared to with insulin. None of the patients treated with dapagliflozin experienced hypoglycemia compared to 5% of patients treated with insulin ($P = 0.0001$). Consistent with our results, Liu *et al*[20] demonstrated that SGLT-2 inhibitors have a minimal risk of hypoglycemia and can cause slight weight loss while reducing BP[20]. The results of our study indicate that dapagliflozin significantly reduced HbA1c levels (from 9.64 to 6.88, 3 months post-treatment), with a P value = 0.0001. Moreover, randomized, double-blind, multicenter, phase 3 trials have demonstrated that dapagliflozin (as monotherapy and combination therapy) effectively enhanced glycemic control and lowered BP and body weight in numerous T2D patients. This includes cases with elevated baseline HbA1c $\geq 9\%$ [21], as well as old cases (aged ≥ 65 years)[22].

Table 5 Comparison of complications rate in the studied groups

Parameter	Dapagliflozin, n = 200	Control group, n = 100	Test of sig.	
			χ^2	P value
UTI	0 (0)	19 (19)	40.569	0.0001
Proteinuria	0 (0)	0 (0)		
Frequent micturition	20 (10)	0 (0)	10.714	0.001
Vertigo	20 (10)	0 (0)	10.714	0.001
Hepatic encephalopathy	0 (0)	6 (6)	6.091	0.014
Variceal bleeding	0 (0)	13 (13)	13.437	0.002
HCC	0 (0)	0 (0)		
Pyelonephritis	0 (0)	0 (0)		
Hypoglycemia	0 (0)	5 (5)	10.169	0.0001
Genital infection	8 (4)	4 (4)	0.098	0.755
Syncope	0 (0)	0 (0)		
Hypotension	12 (6)	5 (5)	0.125	0.724
Dehydration	12 (6)	5 (5)	0.125	0.724
Abdominal discomfort	0 (0)	0 (0)		
Back pain	0 (0)	0 (0)		
Dizziness	0 (0)	0 (0)		
Rash	0 (0)	0 (0)		
Phlebitis	0 (0)	0 (0)		

Data are n (%). HCC: Hepatocellular carcinoma; UTI: Urinary tract infection.

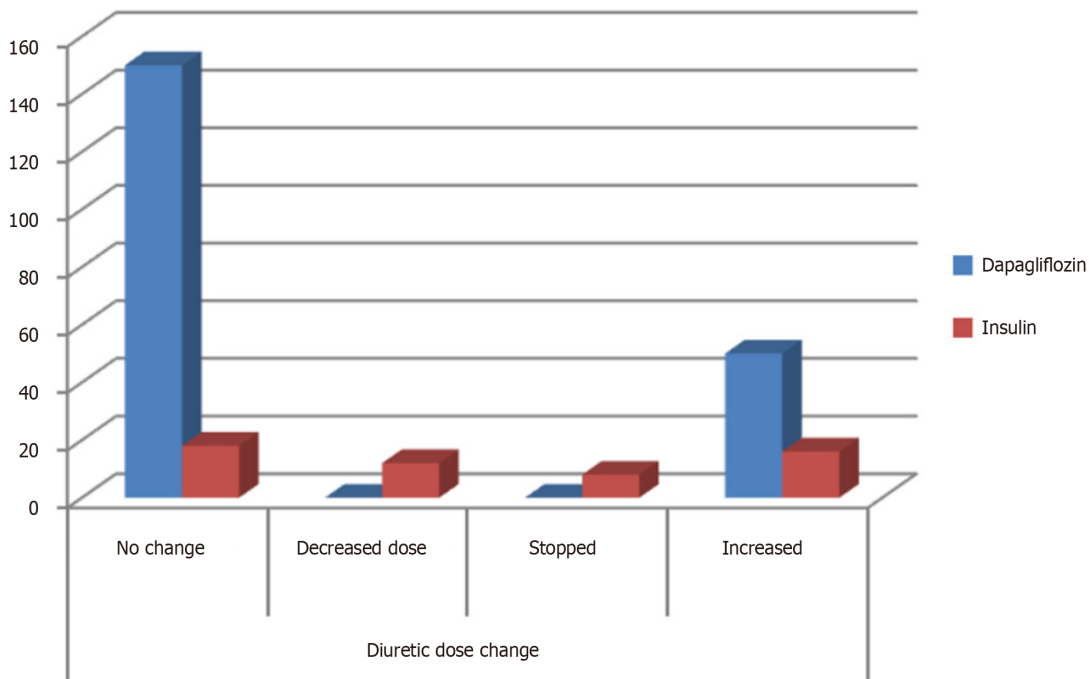


Figure 1 Diuretic dose change in the studied groups.

Regarding the impact of insulin treatment, the present study detected a substantial decline in eGFR, fasting blood glucose, weight, HbA1c, and BMI on follow-up after 3 months in controls treated with insulin. In line with our findings, Mottalib *et al*[23] proved that insulin therapy yields significant clinical advantages, including decreased HbA1c levels and alleviated long-term microvascular complications[23]. In our study, dapagliflozin reduced glomerular filtration rate (GFR) from 125.93 to 116.12, but was statistically non-significant ($P = 0.075$). Meeme and Kasozi demonstrated that glycemic control lowers the GFR in diabetic patients admitted for short-term treatment. A reduction in GFR reflects a reduction of hyperfiltration, a process that starts diabetic nephropathy[24]. Compared to the insulin (control) group, the present study demonstrated a statistically significant reduction in weight, BMI, and fasting blood glucose during the follow-up of dapagliflozin treatment. However, there were no statistically significant differences in HbA1c levels, liver function, or laboratory parameters between the insulin (control) group follow-up and dapagliflozin-treated patients.

In addition, dapagliflozin treatment resulted in a notable enhancement in glycemic control, accompanied by weight reduction, insulin sparing, and reduced occurrence of hypoglycemia compared to insulin therapy[25]. Ahmed *et al*[26] demonstrated that treatment with dapagliflozin resulted in enhancements in various biomarkers, including serum creatinine, blood glucose, serum malondialdehyde, urinary protein, serum urea, urinary glucose level, serum glutathione level, and serum insulin[26]. The present study detected a marked elevation in hepatic encephalopathy, hypoglycemia, UTI in insulin, and variceal bleeding (control group) compared to the treated group. Although frequent urination (experienced by 10% of cases in the dapagliflozin-treated group) and dizziness (experienced by 10% of cases in the dapagliflozin-treated group) were more prevalent in the dapagliflozin-treated group, these side effects were pervasive among females. According to Halimi *et al*[27], the most reported adverse events (AEs) associated with SGLT-2 inhibitors are urinary tract and female genital mycotic infections, increased urination, constipation, and nausea[27].

Similarly, Yen *et al*[28] examined the progression of cirrhotic complications in individuals with compensated cirrhosis who were either using insulin or not. The researchers found that insulin users had a greater likelihood of experiencing variceal bleeding, hepatic encephalopathy, ascites, and hepatic failure compared to those who did not use insulin[28]. Insulin activates adrenergic hormones and triggers the release of endothelin-1[29]. These substances cause the narrowing of blood vessels in isolated arterioles, leading to a rise in both portal pressure and systemic vascular resistance. Cirrhosis can exacerbate insulin resistance and disrupt the molecular insulin mechanisms in hepatocytes. Furthermore, consequent hyperinsulinemia and exogenous insulin may trigger signaling molecules and influence hepatocyte apoptosis[30]. Consequently, they have the potential to exacerbate the progression of LC and result in hepatic failure. Additionally, a prior study revealed that insulin therapy resulted in an elevated susceptibility to hypoglycemia[31].

The present study revealed statistically significantly worse ascites outcomes in the insulin group (controls) than in the dapagliflozin-treated group. In agreement with our results, prior research revealed that SGLT2 inhibitors improved peripheral edema and refractory ascites[5,16]. Furthermore, Kalambokis *et al*[32] documented a case of refractory ascites caused by alcoholic LC that was successfully managed using SGLT2 inhibitors. Before administering an SGLT2 inhibitor, this patient did not respond to the standard diuretics furosemide and spironolactone, and required frequent cell-free and concentrated ascites reinfusion therapy (CART). Nevertheless, the ascites considerably declined upon introducing an SGLT2 inhibitor to manage the patient's hyperglycemia, thereby reducing CART[32]. The present study revealed a marked decline in Child scores following dapagliflozin treatment, but Child classification did not markedly differ. In our research, dapagliflozin treatment decreased Child scores from 7.53 to 7.09, which was statistically significant ($P = 0.0001$). However, there was no alteration in the categorization of children, as the proportions of patients classified as Child A, B, or C remained consistent (28%, 40.5%, 31.5%, respectively) both before and after dapagliflozin treatment. Miyamoto *et al* [33] discovered that enhancing nutritional status may be attributed to a reduction in ascites, leading to decreased abdominal distention and increased food consumption. Moreover, the Child-Pugh score exhibited improvement, indicating enhanced liver function and nutritional status. Nevertheless, there was no statistically significant disparity in the Child's score before and after insulin treatment[33].

In contrast, Yen *et al*[28] demonstrated that individuals who use insulin have a greater likelihood of experiencing hypoglycemia, liver-related complications, cardiovascular events, and mortality when compared to non-users[28]. Dapagliflozin enhances glycemic control and alleviates weight with no increase in major hypoglycemic episodes in cirrhotic cases with DM. In our study, the incidence of UTI was lower in dapagliflozin than in insulin-treated patients. Additionally, 19% of patients in the group receiving insulin treatment experienced UTIs, whereas none receiving dapagliflozin treatment had a statistically significant P value ($P = 0.0001$). In contrast to our study, Zheng *et al*[34] demonstrated that dapagliflozin presented a greater susceptibility to UTIs when compared to both placebo and other active treatments. When using high doses of dapagliflozin for an extended period or when using it as an additional treatment, it is essential to carefully consider the risk of UTI in T2D patients[34]. Our study found that the incidence of genital infection was higher among patients who received dapagliflozin treatment, affecting approximately 4% of those treated with dapagliflozin. In our study, a comprehensive analysis of 13 studies utilizing dapagliflozin revealed no notable rise in the occurrence of renal dysfunction. Genito-UTI is the predominant adverse effect experienced by approximately 5% of patients who receive treatment with dapagliflozin. Most of these infections are uncomplicated genital infections that can be avoided by practicing good hygiene and using antifungal treatment[35]. Additionally, 6% of patients treated with dapagliflozin experienced hypotension and dehydration in our study. Jabbour *et al*[36] found that the incidence of volume depletion (hypotension/hypovolemia/dehydration) was 1.1% and 0.7% with dapagliflozin and placebo, respectively. During the 1st 2 weeks of treatment, 18.5% (5/27) of AEs associated with volume depletion occurred in the dapagliflozin group, while 17.6% (3/17) occurred in the placebo group. When categorized by age, the occurrence of volume depletion was comparable between patients under the age of 65 and those aged ≥ 65 years in the placebo group. However, in the dapagliflozin group, patients ≥ 65 years had a higher likelihood of experiencing volume depletion.

In both treatment groups, the incidence of volume depletion in patients using loop diuretics was 2.5 times greater compared to patients not using them. Furthermore, the occurrence of volume depletion was less common in patients with a baseline eGFR of ≥ 60 mL/min/1.73 m² compared to those with a baseline eGFR of 30 to < 60 mL/min/1.73 m², regardless of the treatment group. Hypotension was the most frequent AE associated with volume depletion in both treatment groups. However, most of these events were deemed unrelated to the study drug, were of mild-to-moderate severity, and did not necessitate the interruption or discontinuation of the drug. Syncope was the second most reported adverse event associated with volume depletion, with episodes thereof occurring at various times during the 24-week treatment period[36]. Yen *et al*[4] demonstrated that SGLT2 inhibitors enhance the excretion of glucose in the urine, reduce blood glucose levels, and alleviate insulin resistance in individuals with T2D. Patients with T2D and mild or moderate liver disease (LD) did not experience any significant alterations in their pharmacokinetic parameters. Nevertheless, it is advisable to exercise caution and administer lower quantities of these substances to patients with cirrhosis, to mitigate the potential dangers of hypotension and dehydration. Co-administering SGLT2 inhibitors with β blockers in patients with LC is likely safe[4]. This study's limitations were the short follow-up period and lack of financial support. The study was done during the endemic coronavirus disease in 2019, which affected the enrollment of more patients.

CONCLUSION

Dapagliflozin demonstrated both safety and efficacy in treating diabetic patients with cirrhosis, regardless of the presence of ascites. The treatment resulted in improved ascites, reduced diuretic dosage, and a lower Child-Pugh score. In our study, the incidence of UTI was lower in the dapagliflozin-treated group, while the incidence of genital infection was higher among patients who received dapagliflozin treatment. Not one of our studied patients complained of nasopharyngitis.

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