Sodium-glucose cotransporter 2 inhibition in patients with liver cirrhosis and diabetes: a possible role in ascites control?

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ABSTRACT

The aim of this brief report is to evaluate sodium-glucose cotransporter 2 inhibitors (SGLT2-I) effects on patients with both refractory ascites and type 2 diabetes mellitus (T2D). We consecutively recruited all the diabetic patients with refractory ascites due to decompensated liver cirrhosis admitted between February and May 2023 at the Internal Medicine Unit of the University Hospital of Palermo. Clinical and laboratory data were collected after starting SGLT2-I therapy. SGLT2-I use was associated with a reduction/resolution of ascites and with an improvement in serum albumin and sodium levels and estimated glomerular filtration rate. SGLT2-I might represent a valid therapeutic option in the treatment of patients with refractory ascites and T2D, as already hypothesized by other research groups.

Introduction

Sodium-glucose cotransporter 2 inhibitors (SGLT2-I), originally developed as an innovative treatment for patients with type 2 diabetes mellitus (T2D),[1] have today become the gold standard in the treatment of patients with cardiovascular disease,[2] heart failure,[3] and chronic kidney disease,[4] and have been included in the treatment guidelines of these conditions.[5,6] T2D is common in patients with liver disease, especially when cirrhosis is related to metabolic dysfunction-associated liver disease (MASLD). Although evidence has proved that SGLT2-I might improve hepatic steatosis and fibrosis,[7] and increase daily urinary volume by increasing sodium and glucose excretion, very few reports have evaluated its effectiveness in patients with ascites due to liver cirrhosis (LC).[8-10]

Here, we report a case series of four patients hospitalized between February and May 2023 in the Internal Medicine Unit of the University Hospital of Palermo, presenting decompensated-ascitic LC and T2D, who were successfully treated with SGLT2-I therapy.

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Materials and Methods

All the diabetic patients, aged >18 years, with refractory or recurrent ascites due to decompensated LC admitted between February and May 2023 at the Internal Medicine Unit of the University Hospital of Palermo were consecutively recruited.

Ascites was defined as refractory or recurrent if dietary sodium restriction and diuretics (both loop diuretics and mineralocorticoid receptor antagonists) were ineffective or caused adverse events [acute kidney failure, portosystemic encephalopathy (PSE), hyponatremia]. All patients were already being treated with metformin. SGLT2-I therapy (dapagliflozin 10 mg/day) was started due to their high cardiovascular risk assessed by SCORE2-diabetes.[11]

Before the start of treatment with SGLT2-I (T0), clinical and laboratory parameters were recorded, and abdominal ultrasonography (US) was performed. Patients then underwent follow-up at 3 months (T1) and 6 months (T2). At each time point, the variables acquired at T0, including abdominal US examination, were reassessed, and the appearance of any adverse events was noted. Further details about the methods are available in the *Supplementary Material*. This case series represents the preliminary part of a larger study registered on ClinicalTrials.gov (Record NCT05999773) and approved by the Ethics Committee of the University Hospital of Palermo (Record 06/2023).

Results

In this preliminary investigation, we recruited eight patients. Four were lost to follow-up and therefore excluded. Of the four patients included in our study, three suffered from MASLD LC, and the fourth had autoimmune LC. Table 1 shows the main clinical and laboratory features of the patients at T0, T1 and T2.

Patient 1, a 76-year-old man with decompensated MASLD LC, under home-based treatment with metformin 1500 mg/day, furosemide 25 mg/day, and canrenone 100 mg/day, was invited to commence dapagliflozin 10 mg/day due to his high cardiovascular risk. At T0, he had grade 3 ascites and Child-Pugh (CP) class B8. Significant weight loss (T0 *versus* T2: 69 *versus* 65 kg) and resolution of ascites at T3 (grade 0) were observed after initiation of SGLT2-I. Natriuresis also increased (T0 *versus* T2: 39 *versus* 178 mEq/L) and hyponatremia resolved (138 mEq/L at T3). During the follow-up, the dosage of furosemide was reduced to 25 mg/3 times weekly because of the resolution of ascites. This and the increase in albumin levels (T0 *versus* T2: 3.4 *versus* 3.8 g/dL) led to an improvement in the CP class.

Patient 2, a 73-year-old woman, was suffering from autoimmune decompensated LC, on home-based treatment with furosemide 50 mg/day and spironolactone 100 mg/day with poor ascites control and intolerance to increased dosage. Dapagliflozin 10 mg/day was started due to her high cardiovascular risk (patient already treated with metformin 1750 mg/day). At T0, she had grade 3 ascites and CP class B7. We observed the resolution of mild hyponatremia (T0 *versus* T2: 133 *versus* 136 mEq/L), increased natriuresis and albumin levels, and weight loss (from 54 to 51 kg). A significant reduction in ascites was also observed, but the CP class remained the same because of increased bilirubin values (T0 *versus* T2: 1.4 *versus* 2.8 mg/dL). The diuretic therapy was reduced to furosemide 25 mg twice a week and canrenone 100 mg/die.

Patient 3, a 65-year-old man with decompensated MASLD LC in CP class B9, intolerant to diuretic therapy due to the appearance of PSE, was treated with dapagliflozin 10 mg/day, added to metformin 750 mg/day. The CP class decreased from B8 to B7 following ascites resolution (T0 grade 3), increased albumin values (T0 *versus* T2: 2.5 *versus* 4.2 g/dL), reduced INR values (from 1.6 to 1.4), but also increased bilirubin values (T0 *versus* T2: 2.9 *versus* 4 mg/dL). In addition, a substantial increase in hemoglobin (Hb) values from 10 g/dL at T0 to 13 g/dL at T2 and a weight loss of 10 kg in 6 months were observed.

Patient 4, a 60-year-old man suffering from decompensated MASLD LC in CP class B8, was treated with dapagliflozin 10 mg/day, metformin 1500 mg/day, furosemide 50 mg/day, and spironolactone 100 mg/day. At T2, a substantial increase in natriuresis (101 mEq/L at T2 *versus* 37 mEq/L at T0) and in albumin values (T2 *versus* T0: 4.3 *versus* 3.4 g/dL), together with weight loss (89 *versus* 96 kg) was observed. At the 6-month follow-up, ascites was no longer detected (at T0 ascites grade 3), with a consequent reduction in CP score from B8 to A5. Therapy with furosemide 50 mg/day was suspended, while therapy with spironolactone 100 mg/day was continued. Of note: Hb values decreased by about 1 g (from 8.3 to 7.2 g/dL), due to the presence of angiodysplasia of the duodenum and colon.

Discussion

Ascites is usually the first clinical manifestation of decompensated LC and significantly worsens the patient's quality of life and prognosis. The cornerstones of ascites treatment are represented by dietary sodium intake restriction and diuretic therapy. However, the drugs currently used have never been shown to improve patient outcomes and may be responsible for the appearance of adverse events such as hyponatremia, hyperkalemia, hypotension, acute renal failure, PSE, and hepatorenal syndrome, which require their suspension. Furthermore, many patients may have recurrent or refractory ascites. In these cases, alternative treatments are still limited and consist of periodic large-volume paracentesis or transjugular intrahepatic portosystemic shunt placement; both these treatments require great patient compliance and are also burdened by a number of complications (*e.g.*, iatrogenic ascites infection, bleeding, PSE, *etc.*).

In this context, SGLT2-I might represent a valid therapeutic option in the treatment of patients with refractory ascites and T2D, as already hypothesized by several research groups.[12]

In our patients, SGLT2-I use was associated with a reduction/resolution of ascites despite the reduction/suspension of conventional diuretics. This result could be explained by the modulatory action that SGLT2-I seem to have on the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), whose hyperactivity determines salt and water retention in patients with LC (a physiopathological mechanism common to heart failure, in which the effectiveness of SGLT2-I has been widely demonstrated).[13]

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Table 1. Clinical and laboratory features of the patients at T0, T1 and T2

	T0	T1	T2
Patient 1			
Ascites grade	3	2	ND
Body weight (kg)	69	67	65
HbA1c (%)	5.8	NA	5.5
Hb (g/dL)	12	12.5	13.2
AST/ALT (U/L)	17/24	18/20	17/22
Bilirubin total/fractionated (mg/dL)	1.9/0.9	1.04/0.6	1.2/0.6
Albumin (g/dL)	3.4	3.6	3.8
INR	1.2	1.12	1.1
Child-Pugh score	B8	A6	A5
Creatinine/eGFR(mg/dL–mL/min)	0.8/92	0.7/95	0.7/95
Natremia/kalemia (mEq/L)	133/4	135/3.8	138/4
Natriuresis (mEq/L)	39	NA	178
Patient 2			
Ascites grade	3	2	1
Body weight (kg)	54	48	51
HbA1c (%)	5.9	NA	5.2
Hb (g/dL)	10	11.5	12.6
AST/ALT	18/15	19/15	17/16
Bilirubin total/fractionated(mg/dL)	1.4/0.5	2.3/1.0	2.8/1.1
Albumin (g/dL)	3.6	3.8	4.0
INR	1.3	1.3	1.3
Child-Pugh score	B7	B7	B7
Creatinine/eGFR(mg/dL–mL/min)	0.7/91	0.6/95	0.6/95
Natremia/kalemia (mEq/L)	133/4	137/4.5	136/4.6
Natriuresis (mEq/L)	46	NA	95
Patient 3			
Ascites grade	3	2	ND
Body weight (kg)	74	65	64
HbA1c (%)	6.1	NA	5.1
Hb (g/dL)	10.4	11.9	13
AST/ALT	21/26	22/25	21/28
Bilirubin total/fractionated (mg/dL)	1.9/1.1	3.9/1.9	4.0/1.9
Albumin (g/dL)	2.5	3.0	4.2
INR	1.6	1.6	1.4
Child-Pugh score	B8	B9	B7
Creatinine/eGFR(mg/dL–mL/min)	0.8/98	0.68/103	0.6/103
Natremia/kalemia (mEq/L)	132/4.6	133/4.6	135/5
Natriuresis (mEq/L)	46	NA	88
Patient 4			
Ascites grade	3	2	ND
Body weight (kg)	96	90	89
HbA1c (%)	6.4	NA	6.0
Hb (g/dL)	8.3	7.4	7.2
AST/ALT	31/29	30/29	30/31
Bilirubin total/fractionated (mg/dL)	1.4/0.7	1.2/0.7	1.1/0.6
Albumin (g/dL)	3.4	4.3	4.3
INR	1.29	1.16	1.16
Child-Pugh score	B8	A6	A5
Creatinine/eGFR(mg/dL–mL/min)	1/86	0.93/94	0.9/94
Natremia/kalemia (mEq/L)	135/4.3	135/4.5	137/4.8
Natriuresis (mEq/L)	37	NA	101

ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, glycated hemoglobin; INR, international normalized ratio; NA, not analyzed; ND, not detectable; T0, before start of sodium-glucose cotransporter 2 inhibitor intake; T1, after 3 months of sodium-glucose cotransporter 2 inhibitor intake; T2, after 6 months of sodium-glucose cotransporter 2 inhibitor intake.

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By interrupting the reabsorption of sodium in the proximal convoluted tubule, SGLT2-I promote a greater concentration of sodium in the macula densa; consequently, the release of renin by the cells of the juxtaglomerular apparatus is inhibited and the activity of the RAAS attenuated.[9]

Another result observed was a mean weight loss of 6±2.5 kg. This could be explained by the natriuretic effect induced by SGLT2-I; the advantage offered by these drugs compared to traditional diuretics is that they promote glycosuria-related osmotic diuresis, which mobilizes liquids from the interstital space, sparing the intravascular compartment. This would make SGLT2-I more advantageous for the treatment of ascites compared to other diuretics, such as loop diuretics, which cause a greater depletion of intravascular fluid with the consequent activation of the RAAS and SNS. Moreover, an improvement in natremia from T0 to T2 was shown in our patients, with a mean ± standard deviation (SD) increase in sodium values of 3.2±1.26 mEq/L, despite a contemporary increase in natriuresis (mean ± SD, 73.5±44.6 mEq/L). Thereafter, lastly, SGLT2-I have been shown to improve hyponatremia without causing hypernatremia after sodium normalization, thus demonstrating a broad safety profile.

Another relevant effect we obtained was a mean ± SD improvement in the estimated glomerular filtration rate of 5±2.1 mL/min (from T0 to T2), calculated according to the Chronic Kidney Disease Epidemiology Collaboration Equation, which is consistent with the literature data demonstrating the nephroprotective effect of SGLT2-I.[14]

SGLT-I therapy might also potentially improve the CP score. In detail, two patients showed a 3-point improvement, while one patient had a 1-point reduction, although in this case, CP remained unmodified due to a worsening of bilirubin values. The CP improvement is probably connected to both the reduction in ascitic effusion and the improvement of albumin values from T0 to T2 (mean ± SD, 0.85±0.61 g/dL). This could be explained by an improvement in the overall nutritional status of patients when using SGLT2-I. This result confirms what had already been reported in another case report in which the administration of SGLT2-I was associated with an increase in serum albumin levels, suggesting an improvement in the patient's liver function and nutritional status.[15]

As is well known, SGLT2-I therapy leads to an improvement in glycometabolic compensation and, consequently, in liver function. We observed a mean ± SD reduction in glycated HbA1c of 0.5±0.18% in 6 months.

Finally, another result that emerged from the observation of patients during therapy with SGLT2-I (except for patient 4, who presented chronic anemia related to multiple gastrointestinal angiodysplasia) was the increase in Hb values. This could be explained by the stimulatory action that SGLT2-I seem to have on erythropoietin release.[16,17] Of note, no adverse events or subjective intolerance were recorded in our patients during the observation period, once again underscoring the safety profile of SGLT2-I, even in cirrhotic patients.

Conclusions

SGLT2-I have pleiotropic properties and multi-organ beneficial effects with an excellent safety profile, even in patients with moderate liver function impairment. Thus, these drugs could represent a valid therapeutic option in the treatment of patients with resistant ascites and T2D. Our brief report proposes to add a small contribution to other reports in the literature, strengthening the basis for a broad and systematic study designed to analyze both the effects and the underlying mechanisms of these drugs in patients with impaired liver function. An observational, prospective, and multicenter case-control study conducted by our research group is currently underway to confirm the promising data of this first case series.

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Online supplementary material:
Supplementary Material. Methods details.