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Sodium Glucose Co-Transporter-2 (Sglt) Inhibitors In Patients With Compensated Cirrhosis And Diabetes: A Prospective Study

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Highlights of the study

1 SGLT-2 inhibitors in cirrhosis and diabetes has not been studied.
2 This study confirms that SGLT-2 inhibitors are safe in patients with compensated cirrhosis with diabetes
3 SGLT-2 inhibitors improve glycemic control and liver function tests in patients with cirrhosis.
4 SGLT-2 inhibitors reduces weight and improves serum creatinine.

1. Abstract

1.1 Aims and objective: Diabetes in patients with cirrhosis is common. SGLT-2 inhibitors are newer class of antidiabetic drugs with pleiotropic effects. Its safety and efficacy has not been evaluated in patients with advanced cirrhosis and diabetes. We evaluated safety and efficacy of SGLT-2 inhibitors in patients with compensated cirrhosis and diabetes.

1.2. Material and method: Consecutive patients with compensated cirrhosis and diabetes who were started on SGLT-2 inhibitors were enrolled and followed every month for six months. Their clinical and biochemical parameters which include liver and kidney function tests, urine test, glycosylated haemoglobin (HbA1c), transient elastography (fibroscan), mean arterial pressure (MAP) and change in weight since treatment initiation were noted. Any relevant side effects (urinary and genital infection, hypotension) were noted.

1.3. Results: Twenty patients [(M:F:13:7), age (55±11yr), CTP score (6±1.3),etiology of cirrhosis (NASH related 17,HBV ,n=1 and HCV, n=2), baseline MAP (91±5 mmHg)] were enrolled. Five patients had hypertension and taking angiotensin converting enzyme (ACE) inhibitors and 15 patients were also on carvidelol. Mean Fibroscan was (37±11kPa), large varices (n=3), small varices (n=16) and no varices were seen in one patient. All patients were followed up for 6 months. Patient were on dapagliflogin (n=11, 55%), empagliflogin (n=6, 30%) and remogliflogin (n=3, 15%). Twelve (60%) patients were also on metformin and 7 (35%) on Dipeptidyl peptidase 4 (DPP4) inhibitors. Significant improvement was seen in total bilirubin [Baseline (B),1.19±0.5, Month 3(Mo 3),1.02±0.4 and Month 6(Mo 6),1.01±0.3 mg/dl], AST (B, 50.8±20.8, Mo 3, 49.4±20.5, Mo 6, 42.8±13.0 IU/L) and GGT(B, 63.8±24.5,Mo3, 66.5±31.0 and Mo 6, 58.3±21.4 IU/dl) level at month 3 and 6. Glycemic index improved at month 3 and 6 and significant weight loss was seen at month 3 and 6. Serum creatinine, serum sodium level and mean arterial pressure remained unchanged at month 6. Urinary tract infection occurred in n=3 (15%), genital infection in (n=2, 10%) and compliant of frothy urine was seen in (n=4,20%) without discontinuation of medicines.

1.4. Results: SGLT-2 inhibitors can be used as newer anti diabetic agent in patients with compensated cirrhosis with diabetes and results in improvement in liver function.

2. Introduction:

One third of patients with cirrhosis have diabetes mellitus. These patients have associated comorbities like hypertension, obesity and dyslipedemia which leads to difficulty in managing these patients [1,2]. Management of diabetes in patients with cirrhosis whether compensated or decompensated is challenging due to safety concerns of available diabetic medications. Cirrhosis patients have reduced capacity to metabolise these drugs and presence of collaterals may lead to higher concentration of these drugs and risk of hypoglycemia. Currently, due to lack of safe pharmacological treatment of diabetes in patients with cirrhosis, insulin is preferred. However, these patients already had insulin resistance and adding insulin might have harmful effect of increased fibrosis and tumourogenic potential [3]. Insulin is also not preferred by many patients and ultimately many patients with cirrhosis and diabetes continued to have high sugar level and lead to complications related to diabetes in these patients. Metformin is commonly used in patients with cirrhosis and in a large cohort of patients it was found to be safe and associated with reduction of overall mortality. Metformin use has also been associated with reduction of Hepatocellular carcinoma and is considered the first line drug in patients with NASH

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related compensated cirrhosis and diabetes [3, 4].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are newer oral medications which are used for the treatment of type 2 diabetes mellitus. These drugs act on SGLT2 receptors in the proximal tubule of the nephron. These drugs promote increased excretion of sodium and glucose in the urine and thereby control glycemic index of the patient [5,6]. These drugs by virtue of its effect on SGLT 2 receptors increase downstream sodium delivery to the macula densa and attenuate renin angiotension aldosterone system (RAAS) pathway and renin secretion. These drugs are now increasingly used as first line drugs in patient with heart failure and kidney disease with or without diabetes due to improvement in overall survival [7-11]. However since their discovery in 2011 these drugs being used rarely in patients with cirrhosis and especially in advanced liver disease due to paucity of data and safety concern like increased chances of hypotension in patients with cirrhosis due to simultaneous use of diuretics, acute renal injury secondary to hypotension, infections and genitourinary tract infections and spontaneous bacterial peritonitis [12, 13]. There are few case reports of use of SGLT-2 inhibitors in patients with cirrhosis to control ascites [14-16]. This observational study was aimed to evaluate the safety and efficacy of SGLT2 inhibitors in patients with diabetes and compensated cirrhosis.

3. Patients and Method

This observational study was done in a tertiary care hospital. All consecutive patients of age more than 18 years who were diagnosed as diabetes and cirrhosis were screened. Patients who were started on SGLT-2 inhibitors within 15 days either alone or in combination with other oral hypoglycaemic medications were enrolled in this study. Patients were excluded from the study if not willing for close follow up, continued to take alcohol, non compliance for regular weight, blood pressure and blood sugar monitoring or taking SGLT-2 inhibitors prior to 15 days of enrollment in the study. Patient with associated portal vein thrombosis, Hepatocellular carcinoma or any sign of decompensation in the past like ascites, variceal bleed and hepatic encephalopathy were also excluded. These patients were followed monthly for at least six months. Cirrhosis was diagnosed based on clinical, biochemical, radiologically parameters and by liver biopsy if available. All patients had Transient elastography [Kpa>14], ultrasound and computed tomography findings consistent with cirrhosis. Diabetes was diagnosed according to standard guidelines or if already taking anti diabetic medications [17].

All patients had baseline upper gastrointestinal endoscopy, liver, kidney functions and other biochemical parameters which includes complete blood count, work up for the etiology of cirrhosis (viral markers, autoimmune analysis, workup for Wilson, hemochromatosis), urine examinations for infection and proteinuria, HbA1c, eye examination, mean arterial pressure and weight. Patients were asked to monitor their blood sugar level, weight and blood pressure at home once a week and keep a diary for it. Patient's liver and kidney functions, urine and HbA1c were monitored at 3 monthly intervals. Patients who were on other medications for associated conditions like hypertension, dyslipedemia or diabetes like beta blockers, statins, anti-viral and other anti-diabetic medications like DPP4 inhibitors, Metformin and insulin were allowed to continue these medications. Written informed consent was taken from patients and the study got approval from hospital ethical committee. During each visit at monthly interval patient MAP, weight, physical examination and any history of side effects like burning micturition, irritation in genital parts or giddiness was asked and noted. Compliance to drugs was also noted. Patient diary was monitored for blood sugar and blood pressure, weight and side effects noted. Patients were free to come at any time in the hospital in case of any problem and side effects.

4. Statistical analysis

The results of this study were expressed as mean± standard error. The p value of < 0.05 was considered statistically significant. Data was compared using the non-parametric Mann–Whitney test for continuous data and Fisher test for categorical data. Comparisons of the variables were performed using the Wilcoxon test and Fisher test as needed. Statistical analyses of the data were performed by using SPSS 10 Statistical Software (SPSS Inc. and Microsoft Corp., Chicago, IL).

5. Results

One hundred and twenty six patients with compensated cirrhosis and diabetes were screened during study period March 2020 to November 2022.One hundred and two patients were excluded as 65 patients had history of previous decompensation of liver disease,5 patients had chronic kidney disease,7 patients had HCC,5 patients had previous SGLT-2 exposure,14 patients did not give consent and 10 patients were not willing for close follow up. Hence twenty patients were enrolled who were started on SGLT-2 inhibitors within 15 days of study enrollement. Of these 20 patients in 12 patients it was started by endocrinologist and in 8 patients it was started by Hepatologist. Twenty patients(M:F:13:7),age(55±11yr) with mean CTP score(6±1.3),etiology of cirrhosis (NASH related 17,HBV ,n=1 and HCV,n=2) and MAP(91±5 mmHg) were enrolled. Mean Fibroscan was (37±11kPa), large varices(n=3), small varices(n=16) and no varices were seen in one patient. These findings suggests that all these patients had clinical significant portal hypertension without any decompensation event (no variceal bleed,no hepatic encephalopathy and no ascites).15 patients were on beta blockers and were taking carvidelol (12.5mg daily). All patients were followed for at least 6 months. Patient were on dapagliflogin (n=11, 55%), empagliflogin (n=6,30%) and remogliflogin (n=3,15%).Twelve (60%) patients were taking metformin and 7(35%) were on DPP4 inhibitors also. Five patients had hypertension and were on telmisartan and it was controlled (Table-1).

Table 1: Baseline characteristics of patients enrolled

Parameters	Mean±SD
Age	55±11
Gender(M:F)	13:7

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Etiology of cirrhosis(NASH:HBV:HCV)	17:1:2
CTP score	6±1
Serum creatinine (mg%)	1.08±0.25
Total bilirubin(mg/dl)	1.19±0.5
Albumin(g/dl)	3.7±0.3
AST(IU/L)	51±21
ALT(IU/L)	43±17
GGT(IU/L)	64±25
Platelet count (10^3/ml)	114±46
HbA1c	7.7±1.1
Fibroscan(kpA)	36.4±11.2
Hb(g/dl)	12±2
MAP(mmHg)	91±4.8

AST: aspartate aminotransferase, ALT: Alanine: aminotransferase, GGT: gamma glutamyl transpeptidase, MAP: mean arterial pressure, Hb: Hemoglobulin

5.1. Follow up data of liver and kidney function test

All patients were followed for 6 months and complete data is available. There is no deterioration in liver function tests from baseline at month 3 and 6. We found significant improvement in serum bilirubin, AST and GGT level at month 3 and 6 compared to baseline however no difference seen between month 3 and 6 between these variables. Similarly there was improvement in serum creatinine at month 3 but not seen at month 6. HbA1c level improved at month 3 and 6 compared to baseline. We also found weight reduction in these patients at month 3 and 6. Weight reduction continued till month 6 of study. We did not find any change in transient elastography as assessed by Fibroscan at baseline and at month 6 (Table-2).

Table2: Follow up data at month 3 and 6

Parameters	Baseline	3 months	6 months	P(B vs 3)	P(B vs 6)	P(3 vs 6 mo)
Total bilirubin(mg/dl)	1.19±0.5	1.02±0.4	1.01±0.3	0.02	0.04	0.7
AST(IU/L)	50.8±20.8	49.4±20.5	42.8±13.0	0.44	0.07	0.008
ALT(IU/L)	42.6±17.1	42.5±17.6	42.6±15.8	0.94	0.52	0.34
Albumin(g/dl)	3.7±0.3	3.6±0.3	3.6±0.4	0.05	0.3	0.83
GGT(IU/L)	63.8±24.5	66.5±31.0	58.3±21.4	0.001	0.8	0.03
Platelet(10^3/ml)	114.6±46.3	125.6±33.9	127.4±27.9	0.03	0.01	0.20
Serum creatinine(mg/dl)	1.08±0.2	1.06±0.25	1.05±0.2	0.002	0.15	0.88
Serum sodium(mmol/l)	137.2±1.7	136.2±1.4	136.1±1.5	0.02	0.04	0.52
MAP(mmHg)	91.1±4.8	87.2±4.5	90.1±4.5	0.001	0.49	0.03
HbA1C	7.79±1.07	7.72±1.05	7.71±0.58	0.001	0.01	0.01
Weight(Kg)	76.6±8.2	74.7±7.3	73.2±7.6	0.001	0.001	0.001
Fibroscan(kPa)	36.4±11.2		35.6±13.0		0.65	

AST: aspartate aminotransferase, ALT: Alanine: aminotransferase, GGT: gamma glutamyl transpeptidase, MAP: mean arterial pressure

5.2. Side effects of SGLT-2 inhibitors in patients with diabetes and cirrhosis

All the patients could tolerate SGLT-2 inhibitors and it was not stopped permanently in any patients due to any side effects. Urinary infection was seen in 3 patients (15%), genital itching in 2(10%), transient giddiness in 2(10%) and frothy urine in 4(20%).

6. Discussion

This prospective study in a selected group of patients with compensated cirrhosis and diabetes showed that SGLT2 inhibitors are effective in controlling diabetes and improve liver function tests. Increasing obesity, poor life style and insulin resistance has become common in all developed and developing nations. Cirrhosis secondary to metabolic dysfunction is rising due to liver steatosis secondary to insulin resistance and availability of better drugs to treat viral etiology. Diabetes is seen in one third of population in some countries and its concurrence with cirrhosis is also common [18,19]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are now an emerging class of medications in the treatment of diabetes mellitus and various non diabetic conditions. It has shown to be useful in patient with congestive heart failure and chronic kidney disease and is used commonly in this condition [9-11]. SGLT-2 induces diuresis due to its natriuresis and osmotic effect. Fluid hemostasis due to SGLT-2 inhibitors effects sympathetic nervous system and renin–angiotensin–aldosterone (RAA) and reduces arginine vasopressin (AVP) and atrial natriuretic peptide (ANP)[5]. However, data on its safety profile and effects on liver function in patients with cirrhosis and diabetes is scarce [14-16].

In our study we found there is significant reduction in total bilirubin, AST and GGT level at 3 months and it persisted till month 6 of treatment.

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Though there was improvement of albumin level at month 3 but we did not find any difference at month 6. These findings suggests improvement in liver function test and improvement in platelet count also suggests that there may be some reduction in portal pressure. We did not measure portal pressure in these patients but it would be of interest to measure HVPG in these patients and know effect of SGLT-2 inhibitors on HVPG. As majority of our patients were also on beta blockers these findings could have been affected by their use in these patients. We did not find any case series or study where systematically liver function tests were monitored after SGLT-2 inhibitors. Few case reports had shown efficacy of SGLT-2 inhibitors in advanced decompensated cirrhosis to relieve ascites and hydrothorax [14-16]. It has been shown in few human and animal studies that SGLT-2 inhibitors improve serum adiponectin level which has got anti inflammatory, anti-apoptotic and anti-fibrotic action [20,21]. We did not measure its level in our study and future trials evaluating anti fibrotic role and improving cirrhosis needs evaluation. We measured Fibroscan at baseline and at 6 months interval but did not found any significant improvement (36.4 ± 11.2 vs 35.6 ± 13.0 kPa,p=ns) but long term data is required for this issue.

6.1. Effect of SGLT-2 on serum sodium and mean arterial pressure: SGLT-2 inhibitors promote glycosuria and causes osmotic diuresis. Increase in urine osmolarity causes more sodium and water in urine to keep urine isotonic. These led to diuresis and change in serum sodium concentration and fluid haemostasis and improve ascites in decompensated patients. In our study we found significant decrease in serum sodium level at month 3 and 6 from 137.2 ± 1.7 at baseline to 136.2 ± 1.4 mmol/dl at month 3 and this change persisted till month 6 (136.1 ± 1.5 mmol/dl).However we did not find any change in serum sodium level between month 3 and 6.In previously published case reports in decompensated cirrhosis serum sodium levels had improved and in patients with normal serum sodium level there was no increase or change in serum sodium level compared to baseline. However these are few case reports and definitive conclusion cannot be drawn based on these case reports [22]. We need further data on compensated and decompensated cirrhosis to come to any conclusion. We found mean arterial pressure to fall initially after SGLT-2 inhibitors in patients with cirrhosis and diabetes and we found significant difference at month 3(91.1 ± 4.8 vs 87.2 ± 4.5 mmHg,p=0.01) however at month 6 we did not find any difference with respect to baseline MAP. It would be worthwhile if we could have measured plasma renin activity and aldosterone concentrations in these patients. There is controversial data on plasma renin and aldosterone level in diabetic patients after starting SGLT-2 inhibitors in presence of ACE inhibitors. These controversial reports may be due to different duration of SGLT-2 inhibitors and with or without ACE inhibitors use. Most of these patients were diabetic with no significant liver disease. Presence of cirrhosis both compensated and decompensated may also affect renin and aldosterone level and this also affect MAP in such combination [23,24]. It will be clarified in future trials focussing on this aspect of hemodyamics in patients with cirrhosis and SGLT-2 inhibitors use.

6.2. Effect on renal function: We find significant reduction in serum creatinine value at 3 month of treatment(1.08 ± 0.2 vs 1.06 ± 0.25 mg/dl,p=0.002) but no difference at 6 month. Similarly no difference was seen between 3 month and 6 month value. Previous studies in patients with diabetes and cardiovascular disease empagliflozin had shown to be renal protective [9-11]. Similarly Dapagliflozin was found to be renal and cardio protective and also effective in reducing all-cause mortality in patients with and without type 2 diabetes [25,26]. However, in patients with cirrhosis its effect on renal functions has not been evaluated properly except in few case reports where renal function did not deteriorate in decompensated patients with cirrhosis.

6.3. Glycaemia control and weight loss: SGLT-2 inhibitors are new class of drugs with modest effect on glycemic control in patients with diabetes and a reduction of 0.5-1% in hemoglobin A1c. However its efficacy in patients with cirrhosis has not been evaluated in a systemic study. In our prospective study we found significant reduction in glycemic index at month3 and 6(p<0.01).This is interesting to find that there was no other significant change in other diabetic medications during this study period and patient compliance was also good during monthly visit assessment.

We find significant weight reduction in these patients and whether it was due to SGLT-2 inhibitors or good compliance and motivation of exercise cannot be assessed as we did not have any control arm [27,28] .However it has been extensively studied in previous various trials and metanalysis in patients with diabetes that SGLT-2 inhibitors reduces weight and it is for the first time that we had also shown that SGLT-2 inhibitors reduces weight even in patients with cirrhosis and improves glysemic control in these patients. It would be of interest to know whether SGLT-2 inhibitors reduces weight in decompensated cirrhosis due to ascites control or true body mass index.

6.4. Side effects of SGLT-2 inhibitors: All our patients could tolerate SGLT-2 inhibitors and it was not stopped during the study period. Frothy urine was told by 20% of our patients and genital infection and urinary infections was seen in 15% of our patients which required treatment and dose modification but we did not stop medication. These patients did not have recurrent infection even after continuing the same dose. In a systemic Meta analysis involving more than 50000 patients with diabetes and SGLT-2 inhibitors it was concluded that SGLT-2 inhibitors are associated with an increased risk of genital tract infections but not with urinary tract infections. Increased risk was seen with higher dose of dapagliflozin [13]. In our study 11 patients were on Dapagliflozin so we found slightly increased frequency of UTI and whether cirrhosis has any inpact on increased frequency of genital infection or urinary tract infection need more data. In conclusion this is probably the first study from Indian subcontinent evaluating the efficacy and safety of SGLT-2 inhibitors in patients with compensated cirrhosis with clinical significant portal hypertension and diabetes. Patients were prospectively followed up and monitored for good compliance and found that SGLT-2 inhibitors can be used in such patient with improvement in liver functions.

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