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Sodium Glucose Transporter 2 Inhibitor as a Novel Therapy for Patients with Chronic Hyponatremia

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ABSTRACT

Background: The most prevalent electrolyte anomaly seen in both hospitalised patients and the general population, hyponatremia is often defined as serum sodium concentration 135 mEq/L and is linked to higher morbidity and death.

Objective: To study sodium glucose transporter2 (SGLT2) Inhibitors influence in individuals suffering euvolemic and hypervolemic chronic hyponatremia and it may be a potential new alternative for persistent hyponatremia therapy in non-diabetic and diabetic patients.

Patients and Methods: That prospective research was carried out on 75 chronic euvolemic or hypervolemic hyponatremia individuals admitted to internal medicine department in hospitals of Benha university. 2 groups were formed from participating individuals: 25 hypervolemic hyponatremia or chronic euvolemic individuals in group (1) who received placebo with additional conventional treatment of chronic hyponatremia (fluid restriction). Group (2) included 50 hypervolemic hyponatremia or chronic euvolemic individuals who received SGLT2 inhibitor (empagliflozin). **Results:** No critical change was seen in serum sodium among day 0 and day 4 or between day 0 and day 30 in SGLT2 inhibitor untreated patients. Serum sodium was critically lower in day 0 than day 4 ($p < 0.001$) and was also substantially lower in day 0 than 30 ($p < 0.001$) in SGLT2 inhibitor treated patients.

Conclusions: The use of SGLT2 inhibitor empagliflozin lead to serum sodium critical elevation in day 4 and 30 after the start of treatment compared to baseline serum sodium level with a higher level at day 4 and 30 than SGLT2 inhibitor untreated patients.

Keywords: Novel Therapy, SGLT2 and Chronic Hyponatremia.

INTRODUCTION

The most common electrolyte problem observed in clinical management is hyponatremia, which is described as a blood sodium content below 135 mEq/L. It may be divided into three types based on extracellular fluid volume: euvolemic, hypervolemic and hypovolemic [1]. Hyponatremia is associated with elevated morbidity, extending between bone problems and elevated risk of fracture to the most severe result of acute hyponatremic encephalopathy, which might need immediate treatment with hypertonic saline [2].

Limiting fluid intake and boosting renal water output are the major aims in managing hyponatremia. This may be achieved by raising urine solute loading, lowering the medullary osmotic gradient regards to water reabsorption, or suppressing ADH activity [3].

Oral hypoglycemic medicines suppress SGLT-2 protein; this is a high-capacity/low-affinity glucose transporter situated in the S1 section of renal proximal tubules and accountable for 90 percent of glucose reabsorption. In diabetic individuals, the production of SGLT-2 increases up to thrice, resulting in a 20 percent rise in glucose reabsorption at a time when the body is actually struggling from blood glucose elevation. SGLT-2 suppression resulted in elimination of 50–60% of filtered glucose, or around 60–100 g per day [4].

On proximal convoluted tubule brush border epithelium are SGLT2 receptors, that are accountable for roughly 90 percent of renal glucose reabsorption in renal tubules [5].

Changes in systolic BP may result from natriuresis, osmotic diuresis, and loss of weight caused by this family of drugs. In addition, SGLT2 inhibitors diminish GFR of a single nephron by causing afferent arteriolar restriction, that results in decreased intraglomerular pressure [6]. SGLT2 inhibitors eliminate fluid preferentially from the interstitium as opposed to the intravascular space, resulting in increased electrolyte-free water removal and enhanced tissue perfusion with no blood volume changing [7].

SGLT-2 inhibitors are strong cardioprotective and nephroprotective medicines, reducing cardiovascular mortality by up to 38%, heart failure hospitalisation by 35%, renal disease progression by 45%, and all-cause mortality by 30% [8].

The aim of the work was to study influence of SGLT-2 Inhibitors in euvolemic and hypervolemic chronic hyponatremia patients and if it could be a potential new alternative for persistent hyponatremia therapy in non-diabetic and diabetic patients.

PATIENTS AND METHODS

That prospective research was carried out on 75 chronic euvolemic or hypervolemic hyponatremia individuals admitted to internal medicine department in Benha university hospitals.

Chronic hyponatremia is hyponatremia which was developed over > 48 h. Hyponatremia is described serum sodium <135 mEq/L and it is classified into 130 – 134 mEq/L for mild hyponatremia, 125 – 129 mEq/L for moderate hyponatremia and <125 mEq/L for severe hyponatremia.

Patients were split into two groups: Group (1): involved 25 with hypervolemic hyponatremia or chronic euvolemic patients who received placebo with additional conventional treatment of chronic

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hyponatremia (fluid restriction), and **Group (2**): included 50 patients with hypervolemic hyponatremia or chronic euvolemic who received SGLT2 inhibitor (empagliflozin).

Inclusion criteria were: age ≥ 18, chronic euvolemic or hypervolemic hyponatremia and Na level < 130 mEq\l.

Exclusion criteria were hypothyroidism, hypocorticism, severe symptoms, individuals requiring 3 percent NaCL solution therapy, hepatic impairment, renal impairment, DM type 1, Systolic BP < 90 mmHg, Peripheral arterio-vascular diseases, pregnancy, breast feeding.

All hospitalized individuals values of plasma sodium were screened daily and oral Empagliflozin (25mg) or placebo were administered daily for four days.

Operational design: All of them were subjected to **Initial assessment: Complete full history taking, including** Age (year), Gender, history of other diseases as liver cirrhosis, renal impairment, of drugs that also cause hyponatremia, history of previous admissions, history of Diabetes (type 1 or type2), history of Hypo or Hyperthyroidism.

Examination: General examination: Vital signs (BP, Temperature, HR, RR), Neck Veins, BMI.

Weight, BMI, BP and Blood and urine sampling were obtained on day 0 (baseline) and then once daily for four days (day 4) following delivery of 25 mg empagliflozin or placebo. 12 and 36 hours following the beginning of the trial, further plasma sodium and glucose tests were performed for safety purposes.

Plasma sodium levels were measured again at discharge and at the planned 30-day follow-up visit following enrolment. At baseline, day 4, and the follow-up session, participant was asked to score their overall wellbeing on a visual analogue scale ranging from 0 (no wellbeing) to 10 (great wellbeing). Individuals were inquired if they have suffered thirst, vertigo, headaches, and nausea with a yes or no response. Variation in plasma sodium value from baseline (day 0) to four days following medication delivery, then daily until patient discharge.

Serum and urine: baseline to day 4, urea, uric acid, and; glucose , urinary sodium and osmolarity and signs of hyponatremia (differ between baseline, day 4 and 30 days).

Local clinical examination: Cardiac, neurological, and chest and abdomen.

Investigations: Serum sodium (reference range is 135-145 mEq/L), Serum potassium (reference range is 3.5 to 5.5 mEq/L), Uric acid (mg/dL)..

Liver Test Profile: AST and ALT, serum albumin, serum bilirubin, GGT, PT and INR.

Albumin Creatinine ratio (mg/dL. Of creatinine). The reference value is < 30 mg/dL.

FBG (mg/dl) fasting blood glucose and PPG (mg/dl) postprandial glucose were determined by the glucose oxidase method based on Trinder.

Reference Values of: Fasting blood glucose: 70-100 mg/dl. Postprandial blood glucose: < 140 mg/dL after two hours of meals. HbA1C (%) Glycosylated Hemoglobin. The normal value range is <5.7%. Serum cholesterol (mg/dl), Serum Triglycerides (mg/dl), HDL cholesterol (mg/dl) and LDL cholesterol (mg/dl).

Reference Values of: Total cholesterol TC < 200mg/dl, HDL cholesterol > 40mg/dl, LDL cholesterol < 100 mg/dl, Triglycerides: <150 mg/dl

Urine concentrations of: Na (mEq/l). The normal range is 40 to 220 mEq/L for 24 hours. Glucose (mg/dl). Normal range is 0 to 15 mg/dL. Creatinine (mg/dl). Normal range for Male = 14 to 26 mg/kg/body weight/day, Female = 11 to 20 mg/kg/body weight/day. Urea (mg/dl). Normal range is 120 – 200 mg/dl. Uric acid (mg/dl). Normal value ranges from 250 to 750 mg/24 hours. Urine osmolarity (mOsm / kg). The normal range is 500 to 850 mOsmol/kg.

Ethical consent:

The study was authorised by Benha University's Ethical Institutional Review Board. All study participants provided written informed permission after being informed of our research's goals. The Declaration of Helsinki for human beings, which is the international medical association's code of ethics, was followed during the conduct of this study.

Statistical analysis

SPSS version 25 performed the statistical analysis (IBM Inc., Chicago, IL, USA). For numerical parametric information, descriptive statistics were calculated as mean SD (standard deviation) and minimum & maximum of the scope; for numerical nonparametric data, descriptive statistics were calculated as median and 1st& 3rd interquartile range; and for categorical data, descriptive statistics were calculated as percentage and number. Analyses of quantitative variables were conducted using the independent t-test for two separate groups with parametric data and the Mann Whitney U for two distinct groups with nonparametric data. For qualitative data, inferences were drawn utilising Chi square test for independent groups. The Wilcoxon Rank test was utilized to analyze the statistical significance change among two non-parametric samples. A two-tailed P value < 0.05 was deemed statistically critical.

RESULTS

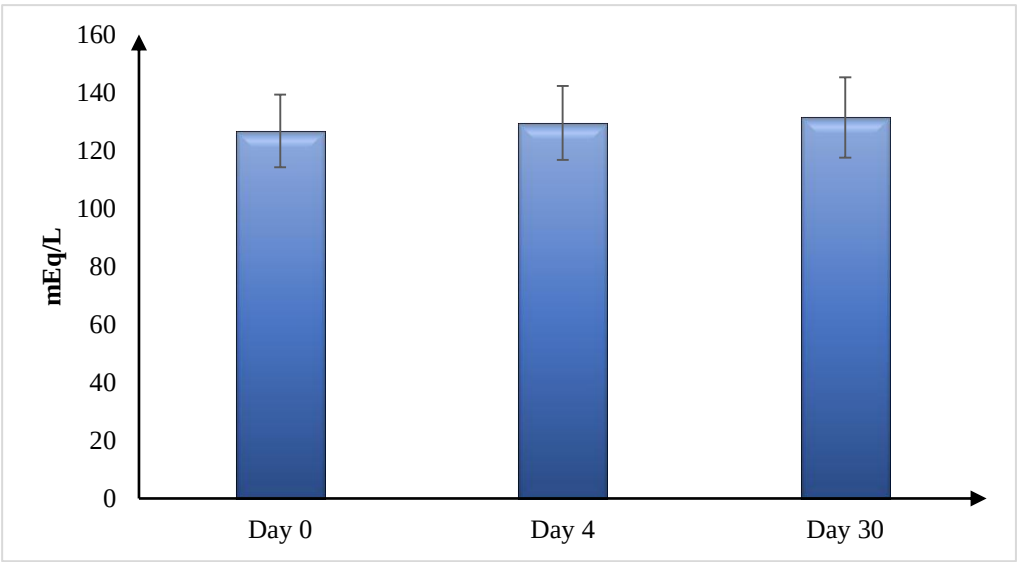
No critical change was seen among groups concerning age, sex, BMI or weight. There was no significant change among groups of study regarding comorbidities and causes of hyponatremia. No critical change was found among study groups concerning symptoms. **Table 1**

Table (1): Demographic characteristics, comorbidities and symptoms among the studied groups.

		Group 1 (n = 25)		Group 2 (n = 50)		P-value
		N	%	N	%	
Sex	Male	10	40 %	20	40 %	0.54
	Female	1 5	60 %	30	60 %	
Age (year)		69.5 ± 3.32		70.6 ± 3.22		0.87
BMI (kg/m^2)		27.20± 2.4		28.98± 2.29		0.06
Weight (Kg)		75.20± 5.4		77.98± 5.29		0.08
Liver cirrhosis		5	20%	10	20%	0.745
Renal impairment		6	24%	14	28%	0.712
History of drugs that also cause Hyponatremia		2	8%	7	14%	0.709
History of previous admissions		3	12%	5	10%	0.519
Diabetes		5	20%	6	12%	0.356
Hypo or Hyperthyroidism		4	16%	8	16%	1.000
Causes of hyponatremia						
Central nervous system disorders		3	12%	4	8%	0.992
Nausea/pain		2	8%	6	12%	
Trauma/postoperative		1	4%	4	8%	
Drug induced		1	4%	2	4%	
Pulmonal disease		4	16%	6	12%	
Infectious diseases		5	20%	10	20%	
Malignant disease		5	20%	10	20%	
Idiopathic		4	16%	8	16%	
Symptoms						
Thirst		2	8.0%	4	8.0%	0.86
Headache		1	4.0%	2	4.0%	0.85
Nausea		2	8.0%	4	8.0%	0.85
Vertigo		2	8.0%	4	8.0%	0.68
General malaise		2	8.0%	4	8.0%	0.59
No		16	64%	32	64%	1.00

P value< 0.05 is significant, P value< 0.01 is highly significant, SD: Standard deviation, Unpaired t-test, X^2= Chi- Square test.

No significant difference was present in serum sodium between day 0 and day 4 or between 0 and 30 days in SGLT2 inhibitor untreated patients. **Figure 1 (A)** Serum sodium was significantly higher in day 4 than 0 (p <0.001) and also was substantially lower in day 0 than day 30 (p <0.001) in SGLT2 inhibitor treated patients. **Figure 1 (B)**



A)

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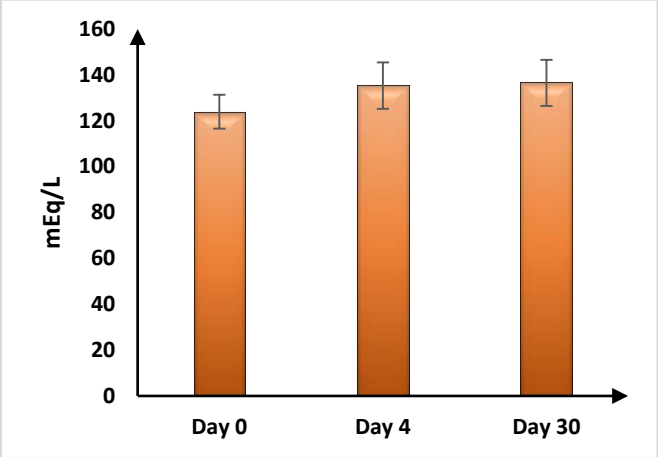

B)

Figure (1): A) Serum sodium level in SGLT2 inhibitor untreated patients and B) Serum sodium level in SGLT2 inhibitor treated patients.

Regarding serum sodium measurements at day zero, 4, and 30, it was significantly lower in group 1 than group 2 at day 4 (p =0.035). no critical change was seen in serum sodium at day 0 and day 30 between the studied groups. **Figure 2**

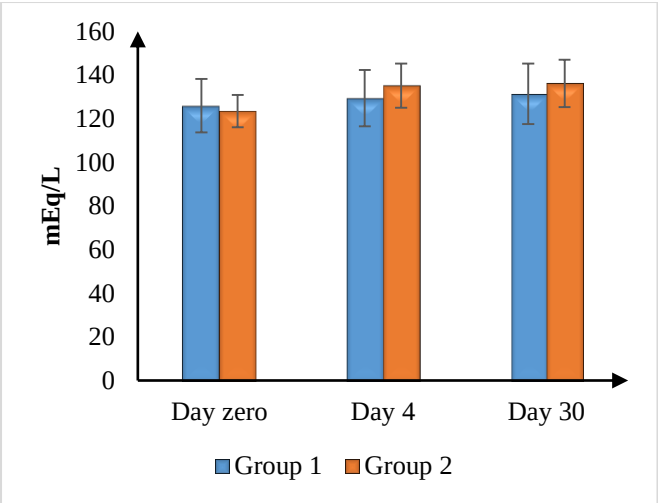

Figure (2): Comparison of serum sodium at day zero, 4, and 30 among the studied groups

Regarding the laboratory results at day zero, no substantial change was seen in serum levels of potassium, glucose, albumin and creatinine among groups of the study. But serum urea and serum uric acid were significantly higher in group 2 than group 1 (p <0.001). Regarding laboratory results at day 4, no substantial change was present in serum potassium concentration, glucose, urea and creatinine among groups of study. But serum albumin was significantly lower in group 1 than 2 (p <0.001) and uric acid concentration was significantly higher in group 1 than 2(p <0.001). Regarding laboratory results at day 30, no critical change was seen in potassium concentration, blood glucose, and urea concentration among groups of study. But serum uric acid and serum creatinine were significantly higher in group 1 than group 2 (p <0.001) and albumin concentration was significantly lower in 1 than 2 group (p <0.001).

Table (2): Baseline laboratory results at day zero, 4 and 30 among the studied groups.

Baseline laboratory results at day zero	Group 1 (n = 25)	Group 2 (n = 50)	P value
Serum potassium (mEq/L)	4.01± 0.20	4.02± 0.20	0.838
Blood Glucose (mg/dL)	6.1± 0.50	6.2± 0.52	0.429
Serum urea (mg/dL)	3.3± 0.32	4.4± 0.21	**<0.001 ***
Serum uric acid (mg/dL)	3± 14.4	217.2± 21.29	**<0.001 ***
Serum Albumin (g/dL)	4.2± 0.4	4.1± 0.35	0.269
Serum Creatinine(mg/dL)	1.01±0.15	1.05±0.19	0.362
Laboratory results at day 4			
Serum potassium (mEq/L)	4.3± 0.40	4.32± 0.40	0.839
Blood Glucose (mg/dL)	108± 7.02	5.3± 0.40	0.068
Serum urea (mg/dL)	4.5± 0.47	4.49 ± 0.31	0.912
Serum uric acid (mg/dL)	3.6± 21.7	181.2± 15.2	**<0.001 ***
Serum Albumin (g/dL)	4.01± 0.35	4.4± 0.45	**<0.001 ***
Serum Creatinine (mg/dL)	1.1±0.2	1.04±0.12	0.109
Laboratory results at day 30			
Serum potassium (mEq/L)	4.4± 0.45	4.55± 0.56	0.248
Blood Glucose (mg/dL)	90± 0.4.5	5.1± 0.25	0.417
Serum urea (mg/dL)	4.8± 0.58	4.8± 0.41	1.000
Serum uric acid (mg/dL)	3.6± 21.9	175.2± 12.2	**<0.001 ***
Serum Albumin (g/dL)	3.9± 0.29	4.8± 0.55	**<0.001 ***
Serum Creatinine (mg/dL)	1.18±0.22	1.01±0.10	**<0.001 ***

P value< 0.05 is significant, P value< 0.01 is highly significant, SD: Standard deviation.

Regarding urinary sodium measurements at day zero, 4, and 30, it was significantly lower in 2 than 1 group at day zero but it was significantly lower in 1 group than 2 at day 30. No critical change was seen in urinary sodium at day 4 among studied groups. **Table 3**

Table (3): Comparison of urinary sodium at day zero, 4, and 30 among the studied groups.

	Group 1 (n = 25)	Group 2 (n = 50)	P value
Day zero	70.2± 7.15	60.4± 6.2	**<0.001***
Day 4	81.2± 8.3	85.2± 8.3	0.053
Day 30	85.2± 9.1	90.5± 9.3	**0.022***

P value< 0.05 is significant, P value< 0.01 is highly significant, SD: Standard deviation.

Regarding urine analysis results at day zero, there was no significant difference in urine glucose, urine urea, and urine osmolarity between the studied groups. But urine uric acid was significantly higher in 2 than 1 group (p <0.001). Regarding urine assessment results at day 4, urine glucose, urine urea, and urine osmolarity were significantly lower in group than group 2. But urine uric acid was significantly lower in group 2 than group 1 (p <0.001). Regarding urine analysis results at day 30, urine glucose, urine urea, and urine osmolarity were significantly lower in group 1 than 2(p<0.001).and urine uric acid was significantly higher in group 1 than 2 (p <0.001). **Table 4**

Table (4): Other urine analysis results at day zero among the studied groups.

At day zero	Group 1 (n = 25)	Group 2 (n = 50)	P value
U-glucose, (mg/dL)	0.0± 0.0	0.0± 0.0	-
U-urea, (mg/dL)	124.1± 12.50	125.2± 12.52	0.721
U-uric acid, (mg/dL)	4.3± .32	1280.4± 110.21	**<0.001***
Urine osmolarity (mOsm / kg)	420.2± 40.4	415.2± 40.4	0.615
At day 4			
U-glucose, (mg/dL)	109± 0.10	110.25± 10.40	**<0.001***
U-urea, (mg/dL)	161.2± 16.2	182.3± 18.40	**<0.001***
U-uric acid, (mg/dL)	3.3± .47	1710.2 ±150.31	**<0.001***
Urine osmolarity (mOsm / kg)	450.2± 43.35	650.2± 64.35	**<0.001***
At day 30			
U-glucose, (mg/dL)	0.45± 0.20	150.25± 15.40	**<0.001***
U-urea, (mg/dL)	178.2± 20.2	198.3± 20.30	**<0.001***
U-uric acid, (mg/dL)	3.6± .47	1850.2 180.31	**<0.001***
Urine osmolarity (mOsm / kg)	480.2± 52.35	720.2± 80.35	**<0.001***

P value< 0.05 is significant, P value< 0.01 is highly significant, SD: Standard deviation.

No statistically significant changes was seen among study groups concerning side effects. **Table 5**

Table (5): Side effects among the studied groups.

Side effects	Group 1 (n = 25)		Group 2 (n = 50)		P-value
	N	%	N	%	
Hypotension	0	0%	2	4%	0.549
Hypoglycemia	3	12%	5	10 %	1.00
Renal impairment	4	16%	6	12 %	0.723
No	18	72%	37	74 %	0.854

P value< 0.05 is significant, P value< 0.01 is highly significant, SD: Standard deviation.

DISCUSSION

Current research revealed that no critical change was seen in serum sodium among day 0 and day 4 or day 30 in SGLT2 inhibitor untreated patients but, sodium concentration was significantly higher in day 4 and day 30compared to day 0 in SGLT2 inhibitor treated patients. Also, serum sodium was significantly lower in group 1 than 2 at day 4. No significant change was seen in serum sodium at day zero and day 30 among study groups.

That was parallel to a study by **Refardt *et al.*** [9] that conducted a double-blind, randomized, crossover trial, placebo-controlled comparing the efficacy of empagliflozin 25 mg/dL over four weeks against placebo in outpatients with persistent hyponatremia. The main endpoint was the change among interventions in serum sodium levels. Following 4 weeks of therapy with empagliflozin, blood sodium levels rose dramatically to a median of 134 mEq/L, but there was no change with placebo. In addition, blood sodium concentrations rose during the first week of therapy with empagliflozin and remained elevated for the remainder of treatment phase, but no significant change was seen with placebo.

Moreover, in **Refardt *et al.*** [10] study**,** the median rise in plasma sodium level after four days of therapy with empagliflozin was 10 mEq/L vs 7 mg/dL with placebo. After 24 hours, the first variation in plasma sodium concentration between treated groups was seen and remained until day 4.

In the present study, at day zero no critical change was seen in serum potassium, blood glucose, serum albumin and creatinine among study groups, but serum urea and serum uric acid were significantly lower in group 1 than 2. At day 4, no substantial change was present in potassium concentration, blood glucose, serum urea and creatinine among groups studied, but serum albumin was significantly lower in group 1 than 2 and serum uric acid was substantially lower in group 2 than 1. At day 30 there was no critical difference in serum potassium, blood glucose, and serum urea between the studied groups, but serum uric acid and serum creatinine were significantly higher in

group 1 than 2 and serum albumin was significantly lower in group 1 than 2.

In **Refardt *et al.*** [9] study**,** no critical change was seen in glucose blood level, urea, and uric acid at end of treatment between empagliflozin and placebo treated individuals, but serum creatinine was significantly increased in patients treated with empagliflozin. During the therapy period, changes began during the first week and persisted until the conclusion of therapy. There was no significant increase in plasma uric acid and plasma urea levels, but plasma glucose was significantly decreased from baseline to the end of treatment.

In present study, urinary sodium was significantly lower in group 2 than 1 at day zero, but it was substantially lower in group 1 than 2 at day 30. No critical change was found in urinary sodium at day 4 among studied groups.

In **Refardt *et al.*** [9] study**,** no critical change was seen in urinary sodium among empagliflozin and placebo managed patients. Also, there were no group differences in urine sodium levels., and it was increased in both groups at day 4 compared to day 0.

In our research, at day zero, no critical change was seen in urine glucose, urine urea, and urine osmolarity between the studied groups, but urine uric acid was significantly lower in group 1 than 2. At day 4, urine glucose, urine urea, and urine osmolality were significantly lower in group 1 than 2, but urine uric acid was substantially higher in group 1 than 2. At day 30, urine glucose, urine urea, and urine osmolarity were significantly lower in group 1 than 2, but urine uric acid was significantly higher in group 1 than 2. In **Refardt *et al.*** [9] study**,** urinary glucose and urine osmolality were significantly higher at end of treatment in individuals treated with empagliflozin compared to patients on placebo, but no critical change was found in urinary urea and urinary uric acid. Also, Individuals in the empagliflozin group had a greater improvement in urine osmolality than those in the placebo group, along with a significant rise in urinary glucose.

There was no statistical difference in adverse effects between the two investigated groups. That is in line with **Refardt *et al.*** [11] who showed no critical change in side effects among individuals who received empagliflozin and patients who received standard therapy. Nevertheless, greater side effects were documented with empagliflozin: 6 vs 2 people needed pain medication for headache, 2 versus none experienced acute vomitus, and 1 participant had transitory severe hypoglycemia of 2.7 mg/dL.

The fact that empagliflozin therapy was better despite the effectiveness of conventional treatment demonstrates its effectiveness. In addition, since long-term compliance with fluid restriction is sometimes restricted, empagliflozin may in the future offer an appealing therapy option for this condition.

Our study's strengths include its prospective, randomised, double-blind design and its innovative treatment strategy.

CONCLUSIONS

SGLT2 is a proximal tubule-expressed protein that reabsorbs roughly 90% of the filtered glucose. The suppression of SGLT2 causes severe glucosuria, followed by increased water output by osmotic diuresis. This process is of great importance since chronic hyponatremia individuals have potential therapy options. Use of SGLT2 inhibitor empagliflozin lead to significant increase in serum sodium in day 4 and day 30 after the start of treatment compared to baseline serum sodium level with a higher level at day 4 and day 30 compared to SGLT2 inhibitor untreated patients. No significant difference in side effects were noted between patients treated with SGLT2 inhibitor empagliflozin and who were not treated.

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