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Evaluation of the clinical value of sodium examination in spot urine in patients presenting with acute heart failure while using SGLT2i – "SPOT HF STUDY"

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ABSTRACT

Objectives: Sodium measurement in spot urine provides important information about the adequacy of the initial dose in acute heart failure (AHF) patients using intravenous diuretic (IV) and makes a guiding contribution to the titration decision. It is not clear whether spot urine sodium measurement has the same clinical value as the effect of sodium-glucose cotransporter 2 inhibitor (SGLT2i) drugs on urinary electrolytes. Our aim in our study is to investigate the clinical value of sodium examination in spot urine in AHF patients while using SGLT2i.

Methods: Our study was conducted retrospectively and single-centered. AHF patients, administered IV diuretics were included in the study. Patients who were using and were not using SGLT2i were examined in two groups. The 2nd and 6th-hour sodium values in spot urine were measured.

Results: Patients using SGLT2i (n = 46) and not using it (n = 54) were included. The mean age was 69.91 ± 11.84 years and 47% were female. The standard deviation value for the sodium in spot urine in patients using SGLT2i was clearly high and its distribution was significantly higher. A weak correlation was found between the sodium value in spot urine and the 24-hour urine volume in this group. Hospitalization history within 1 month after discharge was found to be 39% in the group using SGLT2i, and 51% in the group that did not use it, and this difference was statistically significant.

Conclusions: The measurement of sodium in spot urine does not seem to have the same clinical value in HF patients using SGLT2i. Its correlation with urine volume is also decreasing in this group.

Keywords: Acute heart failure, sodium-glucose cotransporter 2 inhibitor, spot urine

Acute heart failure (AHF) presents a scenario in which rapid response is desired in patients with diuretic treatment requiring decongestion, and numerous factors are considered for dosage adjustments. At this juncture, the titration of diuretic doses and the ability to predict treatment prognosis become crucial.

Among patients hospitalized with acute AHF, nearly 40% face mortality within the first year. A substantial number of patients are also rehospitalized shortly after discharge. In fact, 27% of patients diagnosed with acute AHF return for readmission within the first month [1]. Despite all treatments, one in four

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patients carries residual congestion findings during the discharge phase, which has been associated with a worse prognosis [2, 3]. Consequently, the primary treatment goal of AHF patients is to achieve safe and effective decongestion while reducing early rehospitalization and mortality rates [4, 5].

The tracking of diuretic response commonly relies on measures of input and output, which seem to exhibit a moderate level of consistency [6]. Furthermore, these measurements have limited utility in the context of acute phase treatment titration. Neurohormonal activation triggered by urinary sodium content and antinatriuretic mechanisms eliminates the surprise of diuretic resistance [7, 8]. It has also been demonstrated that effective decongestion resulting from a favorable diuretic response leads to better outcomes [8]. From another perspective, reduced sodium content in urine is associated with higher cardiovascular mortality and hospitalization due to heart failure in patients with acute AHF [9]. At this point, the measurement of spot urine sodium level, which can be utilized within the first 2 hours of treatment, has been reported to exhibit excellent correlation with both the sodium content in urine at the time of examination and the total sodium content in 24-hour urine [10]. Spot urine sodium examination reflects the urinary sodium concentration at the time the urine sample is provided. As highlighted in an important consensus paper published by the Heart Failure Association of the European Society of Cardiology (HFA-ESC), early assessment of spot urine sodium after the initiation of diuretic treatment is recommended for patients with acute heart failure [4].

Based on significant data in heart failure patients, sodium-glucose cotransporter 2 inhibitors (SGLT2i) drugs, which have been strongly recommended, are expected to be prominently featured in the medication regimen for AHF patients in the near future [5]. In this drug class with important outcomes and a range of mechanisms proposed for cardiovascular mortality and rehospitalization due to heart failure [11, 12], the addition of a new player involves mechanisms intertwined with natriuresis and effects on urinary electrolytes. Complex renal interactions and the inhibition of major reabsorption mechanisms such as SGLT2 during the course of sodium reabsorption in renal tubules, followed by compensatory reabsorption mechanisms, result in complex effects on sodium absorption. It is known that natriuresis after usage of SGLT2i results in increased renal vascular resistance, and initial reduction in GFR, due to these effects on urinary sodium content [13]. Given these effects on urinary sodium content, it is not clear whether spot urine sodium measurement, which can be used early in the treatment of AHF patients, holds the same clinical value in this patient group using SGLT2i drugs.

Therefore, the aim of this study is to investigate the clinical value of spot urine sodium examination in patients using SGLT2i drugs while receiving IV diuretic treatment due to acute heart failure.

METHODS

Our study was designed as a retrospective and single-center study, conducted by scanning hospital automation and patient records. The study was planned to include patients admitted to the emergency department between January 1, 2022, and March 1, 2023, who were diagnosed with heart failure, received inpatient care, and underwent 24-hour diuretic therapy. Two groups were formed; patients with SGLT2i and patients not using them. One hundred and five patients not using SGLT2i and 66 patients using SGLT2i were recorded for the study. Patients who have missing laboratory data (n = 29), cardiogenic shock (n = 2), incomplete clinical follow-up (n = 25), acute renal failure (n = 4), glomerular filtration rate (GFR) < 60 mL/min (n = 11) were excluded from the study. Sodium measurements were taken from spot urine samples of all patients at the 2nd and 6th hours.

The Ethics Committee approval was obtained under protocol number 2023/05-13 before the study was initiated.

Patients with a diagnosis of heart failure with reduced ejection fraction (HFrEF) were included in the study if they had been followed for at least 6 months with the diagnosis of HF and at least one month with stable symptoms using guideline-directed medical therapy. Patients diagnosed with AHF who were followed for 24 hours in the intensive care unit (ICU) due to heart failure and received intravenous diuretics were included in the study. The diagnosis of acute heart failure was based on the ESC heart failure guidelines, in patients presenting with signs and symptoms of congestion, requiring intravenous diuretic therapy [5].

Exclusion criteria for the study included in the fol-

lowing: (1) Missing laboratory data, (2) Incomplete clinical follow-up data, (3) Taking medications that could affect the proximal tubule, such as diazoxide, (4) GFR < 60 mL/min, (5) Cardiogenic shock, (6) Acute kidney injury, and (7) Sepsis.

Urinary sodium measurements were performed using the Siemens Advia chemistry XPT device (Siemens®, Germany). Echocardiographic findings of patients were recorded by a cardiology specialist.

Statistical Analysis

The data were recorded in the Statistical Package for the Social Sciences (SPSS, IBM SPSS Statistics for Windows, NY: IBM Corp) 17.0 software package. Normally distributed continuous variables were expressed as mean ± standard deviation, while non-normally distributed variables were expressed as median (minimum-maximum). Categorical variables were presented as numbers and percentages. The signifi-

Table 1. Comparison of demographic data, medical histories, medication usage, and clinical findings of patients in the group using and not using SGLT2i

	SGLT2i group (n = 46)	Non-SGLT2i group (n = 54)	*p* value
Demographic data			
Age (years)	69.76 ± 11.39	70.03 ± 12.22	0.897
Women	21 (45.65%)	26 (48.15%)	0.746
Medical history			
DM	24 (52.17%)	17 (31.48%)	0.545
HT	38 (82.61%)	41 (75.93%)	0.789
HL	13 (28.26%)	14 (25.93%)	0.467
CAD	8 (17.39%)	11 (14.81%)	0.208
COPD	7 (15.22%)	8 (14.81%)	0.387
Medications			
ACEI/ARB	28 (60.86%)	27 (50.00%)	0.771
β-blocker	41 (89.13%)	44 (81.48%)	0.907
ARNI	7 (15.22%)	9 (16.67%)	0.522
MRA	27 (58.70%)	29 (55.77%)	0.884
Furosemide	26 (56.52%)	30 (55.55%)	0.767
Torasemide	12 (26.09%)	13 (24.07%)	0.621
Vital signs			
Systolic blood pressure (mmHg)	140.93 ± 37.18	141,08 ± 35,65	0.923
Diastolic blood pressure (mmHg)	90.75 ± 17.95	89,83 ± 14,69	0.798
Saturation (%)	88.45 ± 3.21	89,11 ± 3,11	0.841
Ejection fraction	37.23 ± 6.25	38,74 ± 7,67	0.632
Intracardiac device	8 (17.39%)	9 (16.67%)	0.441
NIMV	5 (10.87%)	6 (11.11%)	0.912
Inotropic support	3 (6.52%)	2 (3.70%)	0.565

Data are shown as mean±standard deviation or n (%). DM = Diabetes mellitus, HT = Hypertension, HL = Hyperlipidemia, CAD = Coronary artery disease, COPD = Chronic obstructive pulmonary disease, ACEI = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin reseptor blocker, ARNI = Angiotensin reseptor neprilysin inhibitor, MRA = Mineralocorticoid reseptor antagonist, NIMV = Noninvasive mechanical ventilation.

cance of differences between the means of groups with continuous variables was assessed using the Mann-Whitney U test for non-normally distributed groups and the Student's t-test for normally distributed groups. Spearman's correlation test was used to measure the correlation between continuous variables. Pearson's chi-squared test and, when appropriate, Fisher's exact test were used to assess the significance of differences between categorical variables. All calculations were performed as two-tailed tests. Values of $p < 0.05$ were considered statistically significant.

RESULTS

A total of 100 patients, previously diagnosed with acute heart failure (AHF), who were monitored in the intensive care unit (ICU) for 24 hours and received in-

Table 2. Comparison of laboratory data, urine volumes, and admission histories of patients in the group using SGLT2i and the group not using SGLT2i

	SGLT2i group (n = 46)	Non-SGLT2i group (n = 54)	*p* value
Laboratory			
Na (mEq/L)	135.89 ± 4.76	136,45 ± 5.16	0.724
K (mEq/L)	4.12 ± 0.87	3.98 ± 0.79	0.067
BUN (mg/dL)	32.34 ± 9.65	34.74 ± 8.19	0.365
Creatinine (mg/dL)	1.01 ± 0.34	0.98 ± 0.23	0.232
ALT (IU/L)	34.12 ± 13.21	36.33 ± 14.12	0.457
AST (IU/L)	37.78 ± 12.67	38.15 ± 13.29	0.387
WBC ($\times 10^{-3}/\mu L$)	9.34 ± 5.67	8.87 ± 6.71	0.105
Hb (g/dL)	13.25 ± 2.13	12.98 ± 2.58	0.656
Htc (%)	39.87 ± 7.12	38.91 ± 7.52	0.545
PLT ($\times 10^{-3}/\mu L$)	211.12 ± 67.32	198.59 ± 71.13	0.189
eGFR (mL/min)	62.48 ± 12.78	64.12 ± 13.32	0.754
TSH (mU/mL)	3.24 ± 1.01	3.18 ± 0.98	0.841
BNP (pg/mL)	701.22 ± 132.84	69716 ± 143.62	0.789
Spot urine sodium			
2nd hour	79.45 ± 44.12	82,13 ± 18.95	0.245
6th hour	64.54 ± 31.02	62,10 ± 11.89	0.365
Urine volume			
1st hour	209.07 ± 39.40	214.12 ± 48.64	0.089
2nd hour	181.22 ± 29.78	187.88 ± 31.11	0.105
3rd hour	170.03 ± 28.57	173.46 ± 29.97	0.242
24 hour	2734.23 ± 876.71	2813.55 ± 965.23	0.211
Diuretic dose			
Initially	85.12 ± 23.41	82.89 ± 19.87	0.221
24 hour	148.34 ± 43.47	144.73 ± 38.89	0.423
Rehospitalization in the first month	18 (39.13%)	28 (51.85%)	**< 0.001**

Data are shown as mean±standard deviation or n (%). Na= sodium, K = potassium, BUN = blood urea nitrogen, ALT = alanine transaminase, AST = aspartate transferase, WBC = white blood cell, Hb = hemoglobin, Htc = hematocrit, PLT = platelets, eGFR = estimated glomerular filtration rate, TSH = throid stimulating hormone, BNP = brain natriuretic peptide

travenous diuretic therapy, were included in the study. Among these patients, 46 were using SGLT2i and 54 were not using them. The mean age of the patients evaluated in the study was 69.91 ± 11.84 years, with an age range of 53 to 88. Among the included patients, 47% (47) were female.

When comparing patients using SGLT2i with those not using it, there were no significant differences in terms of age and gender. The most common comorbidity was hypertension (HT) in their medical history (n = 79). The numbers of patients with comorbidities like HT, diabetes mellitus (DM), hyperlipidemia (HL), coronary artery disease (CAD), and chronic obstructive pulmonary disease (COPD) were similar between the two groups. There was no significant difference between the two groups in terms of pre-admission medication use (beta-blockers, angiotensin-converting enzyme inhibitors, mineralocorticoid reseptor antagonists, angiotensin reseptor neprilysin inhibitors, furosemide, or torasemide). Vital signs at the time of admission were similar in both groups. There was no significant difference between the two groups in the use of noninvasive mechanical ventilation (NIMV) and inotropic support during acute admission. The echocardiographic findings, including ejection fraction (EF) values and intracardiac device usage, were not statistically significantly different between the two groups (Table 1).

Hematological parameters, biochemical results, and B-type natriuretic peptide (BNP) levels were similar between the SGLT2i-using and non-using groups. While sodium levels measured in spot urine at 2 hours and 6 hours were lower in the SGLT2i-using group, this difference was not statistically significant. Urine output volumes did not differ between the two groups. The diuretic doses used in both groups were similar. Within 1 month after discharge, the history of readmission was observed in 18 patients (39.13%) in the SGLT2i-using group and 28 (51.85%) patients in the non-using group, with this difference being statistically significant ($p < 0.001$) (Table 2).

Upon detailed analysis of sodium values measured in spot urine at 2 hours, it is noteworthy that the SGLT2i using group had a quite higher standard deviation value (79.45 ± 44.12). The distribution of sodium values measured in spot urine at 2 hours for the patients included in the study is graphically represented in Fig. 1 and Fig. 2. The distribution in the SGLT2i-using group appears to be significantly wider compared to the other group.

In patients using SGLT2i, both the 2nd and 6th-hour sodium values in spot urine exhibited weak correlations with the 24-hour urine volumes. In contrast, in patients not using SGLT2i, both the 2nd and 6th-hour sodium values in spot urine showed strong correlations with the 24-hour urine volumes (Table 3).

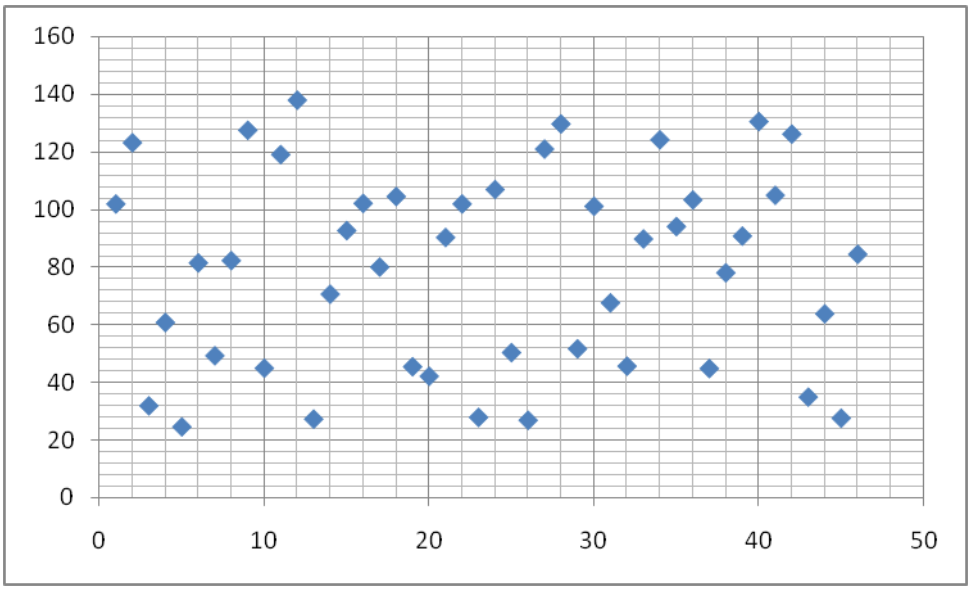

Fig. 1. Distribution of sodium values measured within the first 2 hours in patients using SGLT2 inhibitors.

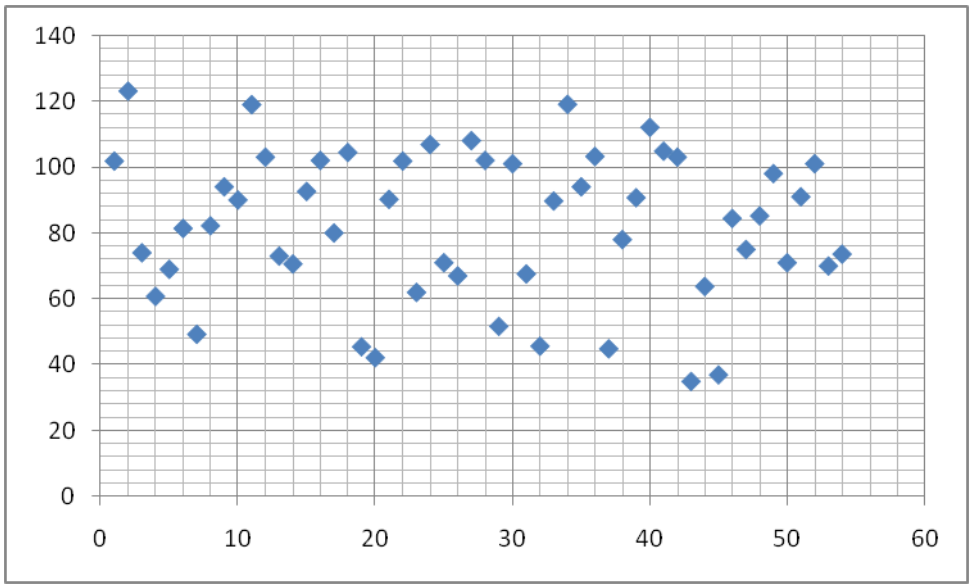

Fig. 2. Distribution of sodium values measured within the first 2 hours in patients not using SGLT2 inhibitors. .

DISCUSSION

The main finding of this study is that the clinical value of spot urine sodium measurement, an indicator of diuretic response, is significantly compromised in patients using SGLT2i and receiving IV diuretic therapy for AHF. Another important result is that the spot urine sodium value measured at 2 hours has a strong correlation with the 24-hour urine volume in patients not using SGLT2i, whereas this correlation is absent in patients using SGLT2i. Finally, patients using SGLT2i showed significantly fewer readmissions within one month.

In acute heart failure patients, urine volume and sodium content have attracted attention in terms of treatment response and prognosis. While negative fluid balance is one of the prominent monitoring tools in clinical practice, urinary sodium appears to be a cornerstone of this topic. In fact, some studies concluded that urine volume was not associated with survival but sodium excretion was [14], whereas a study showed that urine volume and sodium excretion were not correlated [15]. Yet another study suggested that the prognostic importance of urinary sodium excretion in acute heart failure patients changes with the use of mineralocorticoid receptor antagonists (MRAs), including spironolactone [16]. However, the challenges of consistent collection and measurement of urine have also been highlighted in studies [6, 17].

In light of these debates, contemporary guidelines have recognized urinary sodium excretion and its measurement through spot urine as a clear recommendation in AHF patients [5]. The advantages of being able to assess sodium in spot urine early in treatment

Table 3. Correlation between spot urinary sodium levels and 24-hour urine volume in the group using and not using SGLT2i

	24-hour urine volume	
	SGLT2i group	**Non-SGLT2i group**
2nd hour spot urine sodium	$p = 0.141$	$\mathbf{p < 0.001}$
	r:0.237	r: 0.772
6th hour spot urine sodium	$p = 0.102$	$\mathbf{p < 0.001}$
	r:0.262	r: 0.746

and its ease of measurement have strongly supported the measurement of sodium in spot urine. When introduced into the scientific discourse, a study has demonstrated that spot urine sodium measurement significantly reduces urine volume and the occurrence of rehospitalization and emergency department visits within one month [18]. The study by Testani et al. [10] showed that spot urine sodium measurement at 1 or 2 hours provides robust data for predicting subsequent poor diuretic response.

However, in none of these mentioned studies, the inclusion of a potent new player, SGLT2i, which is involved in heart failure treatment and can impact urinary sodium, has been investigated. With the added contribution of spot urine sodium measurement and the potential effect of SGLT2i, in addition to loop diuretics' impact on urinary sodium, it remains unclear whether this measurement will retain the same clinical value.

SGLT2i drugs have emerged as an important drug group that reduces hospitalization due to HF, demonstrating this effect in both heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) patients. The fact that these effects are observed in both diabetic and non-diabetic patient groups implies the introduction of an effective instrument into heart failure treatment [11, 12, 19]. While the mechanisms are not fully understood, being a diuretic or natriuretic agent is an inevitable assumption. In the proximal tubule, for every glucose molecule absorbed, one sodium ion is absorbed due to the significant effect of the SGLT2 transporter. If sodium is not absorbed here, absorption continues in the segments after the proximal tubule through SGLT1 and Na-H exchangers [20]. Since the majority of this absorption occurs through SGLT2, other mechanisms are suppressed in normal physiology. With the reduction of sodium absorption in the proximal tubule due to SGLT2i, the amount of sodium reaching the macula densa increases, leading to vasoconstriction of afferent arterioles and consequently a decrease in glomerular pressure, resulting in hyperfiltration [21]. The extent to which natriuresis can be compensated for due to these complex effects is not clear, but it is known that the activities of SGLT1 and NHE3 cannot fully compensate for this effect [22]. In a simplified perspective, expecting a clear effect towards natriuresis is reasonable. However, there are much more complex intrarenal effects and interactions with drugs such as loop diuretics that affect this region [23]. As a result, the effects on urinary sodium and many related electrolytes may diminish the decision-making ability in tests that measure these parameters.

In the study by Griffin et al. [24], empagliflozin was compared to placebo, and it significantly increased fractional sodium excretion. This effect was found to be synergistic when combined with bumetanide. As a result, empagliflozin induced effective natriuresis and potentiated this effect when combined with loop diuretics. Furthermore, in conjunction with this effect, there was no increase in neurohormonal activity, electrolyte wasting, or renal dysfunction observed. Although the natriuretic effect of SGLT2i was evaluated in this study, the study population consisted of stable HF patients. Another study demonstrated that the addition of empagliflozin to early treatment in acute HF increased cumulative diuresis after four days, leading to a reduction in HF-related events [25]. In another significant study, acute HF patients were divided into empagliflozin and placebo groups. While there was no difference in spot urine sodium levels between the two groups at admission, a significant reduction in spot urine sodium levels was observed, especially at 48 hours, in the empagliflozin group [26]. In the same study, FeNa and FeCl did not change between the two groups, but plasma osmolality increased. Urine volume increased, but urine osmolality remained unchanged. All of these findings suggest that the effect of SGLT2i treatment on electrolytes and urine, as well as the response of renal tubule physiology, is complex and multifaceted.

The confusing effect of SGLT2i on sodium is further enriched by some studies. For example, dapagliflozin has been shown to reduce tissue sodium in type 2 DM patients, in addition to inducing natriuresis and glucosuria [27]. Another study indicates significant evidence that SGLT2i agents bind to Na-H exchanger 1 (NHE) receptors in the myocardium as inhibitors (28). Indeed, these exchanger isoforms are also present in the kidney. In another study using dapagliflozin, it was demonstrated that while dermal tissue sodium decreased with treatment, serum sodium, and 24-hour urine sodium excretion did not change compared to placebo [27]. In a study with canagliflozin, it was shown that canagliflozin use increased urine sodium excretion and correlated with in-

creased urine volume on the first day [29]. However, this effect was not observed from the second day onwards, further complicating the interpretation of its effect on urine sodium. Another perspective is that in this study, the natriuretic effect of diuresis was more related to natriuresis than the osmotic effect of glucosuria. Other studies have also suggested an inverse correlation between natriuretic and glucosuric effects [24].

The confusing effect of SGLT2i on sodium is further enriched by some studies. For example, dapagliflozin has been shown to reduce tissue sodium in T2DM patients, in addition to inducing natriuresis and glucosuria [27]. Another study indicates significant evidence that SGLT2i agents bind to Na-H exchanger 1 (NHE) receptors in the myocardium as inhibitors [28]. Indeed, these exchanger isoforms are also present in the kidney. In another study using dapagliflozin, it was demonstrated that while dermal tissue sodium decreased with treatment, serum sodium and 24-hour urine sodium excretion did not change compared to placebo [27]. In a study with canagliflozin, it was shown that canagliflozin use increased urine sodium excretion and correlated with increased urine volume on the first day [29]. However, this effect was not observed from the second day onwards, further complicating the interpretation of its effect on urine sodium. Another perspective is that in this study, the natriuretic effect of diuresis was more related to natriuresis than the osmotic effect of glucosuria. Other studies have also suggested an inverse correlation between natriuretic and glucosuric effects [24].

The positive impact of SGLT2i use on hospitalization due to HF has been clearly demonstrated. Moreover, this effect has been shown to be independent of the presence of DM [11, 12]. Whether in the presence or absence of chronic kidney disease (CKD), the beneficial effects of SGLT2i on cardiovascular outcomes and HF-related hospitalizations have been clearly established [32-34]. In a study involving acute HF patients, the empagliflozin arm showed a significant increase in urine output compared to the placebo arm, resulting in a much stronger negative fluid balance [26]. The use of dapagliflozin, with or without diuretics, has been found to be safe and effective [19]. The impact of SGLT2i use on a more profound negative fluid balance, tissue sodium, and the interstitial space has been demonstrated [25, 35].

Considering all the impacts on HF and based on all these data, it does not seem surprising that the hospitalization duration is significantly shorter in the group using SGLT2i, as we observed in our study.

CONCLUSION

Spot urinary sodium analysis is an effective tool that can be utilized in the early stages of treatment for AHF patients. Its correlation with urine volume further reinforces its significance. In this patient group, the examination of spot urinary sodium, which will increasingly find a place in evaluating the diuretic response, becomes crucial. The results of our study are also important in demonstrating that the same spot urinary sodium analysis, which will progressively become more common in assessing diuretic response in this patient population, does not have a similar clinical impact in individuals using SGLT2 inhibitors. This outcome will significantly contribute to the clinical perspective. We believe that these results provide guiding insights for subsequent larger-scale studies that can be conducted in this patient group.

Authors' Contribution

Study Conception: OA; Study Design: OA; Supervision: OA; Funding: OA, EED; Materials: EED; Data Collection and/or Processing: OA, EED; Statistical Analysis and/or Data Interpretation: OA; Literature Review: OA, EED; Manuscript Preparation: OA, EED and Critical Review: OA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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