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Clinical Research Article

Prevalence of Admission Hyponatremia in Patients With Diabetes Treated With and Without an SGLT2 inhibitor

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Abstract

Context: Hyponatremia often reflects a free water excess. Sodium/glucose cotransporter 2 (SGLT2) inhibitors increase free water excretion through glucose-induced osmotic diuresis. In 2 randomized double-blind, placebo-controlled trials in patients with the syndrome of inappropriate antidiuresis (SIAD), we showed that empagliflozin increased plasma sodium concentration more effectively than placebo.

Objective: We hypothesized that long-term therapy with SGLT2 inhibitors might reduce the prevalence of hyponatremia on hospital admission.

Methods: In this retrospective analysis, we extracted data from adult patients with type 2 diabetes (T2DM) hospitalized at the University Hospital Basel between 2015 and 2020. Patients with an SGLT2 inhibitor on admission were matched 1:1 according to age, gender, diagnosis of heart failure, and principal diagnosis to patients without an SGLT2 inhibitor on admission. The primary outcome was the prevalence of hyponatremia (plasma sodium concentration corrected for glycemia <135 mmol/L) on admission.

Results: We analyzed 821 patients with T2DM treated with and 821 patients with T2DM without an SGLT2 inhibitor on admission. Hyponatremia prevalence on admission was 9.9% in the treated group, and 8.9% in the matched control group ($P = .554$), in other words, the risk for hyponatremia did not differ (multivariable adjusted odds ratio 1.08, 95% CI 0.72-1.44, $P = .666$). There was no difference in the median (interquartile range) plasma sodium concentration between the groups (treated 140 mmol/L [138-142], controls 140 mmol/L [138-142]; $P = .1017$).

Conclusion: Based on these retrospective findings, treatment with SGLT2 inhibitors does not prevent hyponatremia. However, prospective randomized data suggest their efficacy at a higher dosage in overt SIAD.

Key Words: sodium/glucose cotransporter 2 inhibitor, type 2 diabetes, hyponatremia, dysnatremia

Abbreviations: AVP, arginine vasopressin; HFrEF, heart failure and reduced ejection fraction; IQR, interquartile range; SGLT2, sodium/glucose cotransporter 2; SIAD, syndrome of inappropriate antidiuresis; T2DM, type 2 diabetes.

Hyponatremia, defined as plasma sodium concentration <135 mmol/L, is the most common electrolyte disturbance in hospitalized patients [1]. Its prevalence on hospital admission ranges from 3% to 38%, depending on the severity of hyponatremia [1-4]. Hyponatremia on hospital admission is associated with increased in-hospital [1, 2, 4], 1-year [2, 5], and 5-year mortality [2]. Furthermore, it is associated with an increased risk for intensive care unit admission and mechanical ventilation [3], longer hospital stays [3, 4], higher hospital costs [3], and discharge to care facilities [4].

In prevailing guidelines, treatments for hypovolemic hyponatremia and acute severely symptomatic hyponatremia are well established [6-8]. By contrast, patients with chronic euvolemic or hypervolemic hyponatremia are often discharged still hyponatremic because of the limited efficacy of the available therapeutic options [9].

Both euvolemic and hypervolemic hyponatremia result primarily from arginine vasopressin (AVP)–mediated free water retention [10]. Accordingly, fluid restriction is usually the first-line therapy but has limited efficacy [11]. AVP antagonists (vaptans) lead to increased aquaresis and can be used as a second-line treatment [6, 8, 12, 13]. However, they are costly and carry the risk for overly rapid plasma sodium correction, requiring close plasma sodium monitoring on treatment initiation [14-16].

The sodium/glucose cotransporter 2 (SGLT2) is expressed in the proximal tubules of the kidneys and reabsorbs approximately 90% of the filtered glucose [17]. Blockade of SGLT2 with SGLT2 inhibitors (oral antidiabetic drugs) results in renal excretion of glucose [18] and subsequent osmotic diuresis [19]. The SGLT2 inhibitor empagliflozin reduces the risk of major adverse cardiovascular events [20] and heart failure [21] and slows progression of kidney disease in patients with diabetes with high cardiovascular risk [22]. Empagliflozin has also cardiovascular and renal benefits regardless of diabetes mellitus in patients with heart failure and reduced ejection fraction (HFrEF) [23] or heart failure

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and preserved ejection fraction [24]. Furthermore, we showed in a randomized, double-blind, placebo-controlled trial in 87 hospitalized euvolemic hyponatremic patients with the syndrome of inappropriate antidiuresis (SIAD) that a 4-day treatment with empagliflozin combined with fluid restriction led to a higher plasma sodium increase than fluid restriction alone [25]. We recently confirmed these findings in a randomized, double-blind, placebo-controlled, crossover trial in 14 outpatients with chronic SIAD [26].

To our knowledge, the effect of long-term treatment with SGLT2 inhibitors on hyponatremia prevalence in hospitalized patients has never been investigated. We aimed to compare hyponatremia prevalence on admission in patients with type 2 diabetes (T2DM) treated with an SGLT2 inhibitor with that in control patients with T2DM but without SGLT2 inhibitors. We hypothesized that hyponatremia prevalence is lower in patients treated with an SGLT2 inhibitor. This would support their use as a prophylaxis for hyponatremia recurrence in patients with chronic hyponatremia or as a prophylaxis for hyponatremia in general in at-risk patients.

Materials and Methods

Patients Selection and Extraction

This retrospective, cross-sectional study selected all patients with (T2DM) hospitalized at the University Hospital of Basel, Switzerland, between 2015 and 2020 with available plasma sodium measurement within the first 24 hours following admission (Fig. 1). Demographic characteristics, medication on admission, plasma glucose and osmolality (if available at the timepoint of sodium measurement), and comorbidities were extracted from the electronic health records at the same time by the Information and Communication Technologies Department of the University Hospital of Basel and transmitted to the first author for statistical analysis. Diagnoses were coded with the International Statistical Classification of Diseases and Related Health Problems (ICD) 10-GM (version 2014, 2016, and 2018) [27-29] and taken from discharge reports. The extraction of the health-related data from the electronic health records of the University Hospital of Basel required for this study was approved by the local ethics committee (Ethikkommision Nordwest- und Zentralschweiz, EKNZ 2021-00649).

Laboratory

Plasma concentrations of sodium, glucose, and osmolality were from the same timepoint and measured by the central laboratory of the University Hospital Basel. Plasma sodium concentration was measured by the indirect ion selective electrode (ISE) method (cobas 8000 modular analyzer, Roche Diagnostics) in centrifuged lithium–heparin plasma. Plasma osmolality levels were measured using the freezing point depression osmometric method.

At higher concentrations, glucose can cause translocational isotonic or hypertonic hyponatremia [30]. Because all selected patients were diabetic, we corrected plasma sodium values for glycemia according to the linear model of Hillier et al [30], as recommended by European guidelines [6]. For each patient with glycemia above 5.5 mmol/L, sodium levels were corrected by adding 2.4 mmol/L per 5.5 mmol/L glucose using the following equation:

$$\begin{aligned}&\text{Corrected sodium levels (mmol/L)}\\&= \text{measured sodium levels (mmol/L)} + 2.4\\&\times \frac{\text{glucose levels (mmol/L)} - 5.5\ \text{mmol/L}}{5.5\ \text{mmol/L}}\end{aligned}$$

Hyponatremia was defined as a plasma sodium concentration <135 mmol/L and further subclassified according to biochemical severity (mild, plasma sodium concentration 130-134 mmol/L; moderate, plasma sodium concentration 125-129 mmol/L; profound, plasma sodium concentration <125 mmol/L) [6]. Hypernatremia was defined as a plasma sodium concentration >145 mmol/L.

Study Outcomes

The primary outcome was the prevalence of hyponatremia on hospital admission in patients with T2DM treated with an SGLT2 inhibitor vs matched control patients with T2DM without an SGLT2 inhibitor.

The secondary outcomes included the difference in plasma sodium concentration, the prevalence of hyponatremia severities, and hypernatremia in patients with T2DM treated with an SGLT2 inhibitor vs matched control patients with T2DM who were not treated with an SGLT2 inhibitor. We additionally computed the prevalence of hyponatremia, hyponatremia severities, and hypernatremia in a subset excluding patients with an ICD10 code for hypovolemia or hypotension and in a subset containing only patients with hypervolemia with heart failure, chronic kidney disease, or liver cirrhosis as a comorbidity. Furthermore, we investigated the association between SGLT2 inhibitors and hyponatremia on admission adjusted for medication and comorbidities, as well as whether SGLT2 inhibitors have an influence on plasma sodium levels when adjusted for medication and comorbidities.

Statistical Analysis

Baseline characteristics are summarized using descriptive statistics. Discrete variables are expressed as frequencies (% and number of patients, n). Continuous variables are expressed as median and interquartile range (IQR, 25th to 75th percentiles).

Eight hundred twenty-one patients treated with an SGLT2 inhibitor, and 15 999 control patients met the selection criteria. We performed 1:1 propensity score matching using the package *MatchIt* [31]. The average treatment effect on the treated (ATT) was estimated by fitting a generalized linear model with the variable SGLT2 inhibitor as the dependent variable and the covariates gender, age (±5 years), heart failure diagnosis, and main diagnosis (as ICD10 chapter) as independent variables. Patients were matched 1:1 using the nearest neighbor matching (ie, "greedy matching") method without replacement; therefore, each treated patient was matched to 1 control patient and 15 178 controls were discarded. Further details on matching specification and covariate balance can be found elsewhere [32].

Prevalence in each group was compared using the chi-squared test. Plasma sodium concentration in each group was compared using the Wilcoxon–Mann–Whitney test. The independent effect of SGLT2 inhibitors on hyponatremia occurrence on admission was investigated by fitting a univariable and a multivariable logistic regression model. The

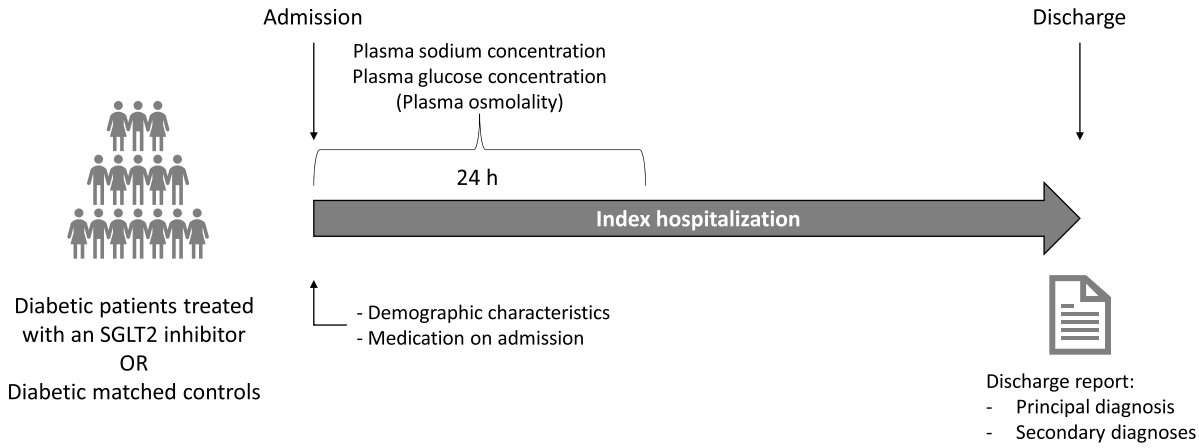

Figure 1. Study diagram. Study diagram showing patients selection. All patients with type 2 diabetes hospitalized between 2015 and 2020 and with a plasma sodium and a glucose measurement within the first 24 hours following admission were selected.

model with the lowest Akaike information criterion was selected in a stepwise way using the *step* function, with SGLT2 inhibitors as a fixed predictor [33]. The association between plasma sodium concentration and SGLT2 inhibitors was investigated in the same way, in other words, with a univariable and multivariable linear model, with additional verification of assumptions and multicollinearity. Detailed covariables fitting and outputs can be found elsewhere [32].

All analyses were performed using the statistical program R (version 4.0.5 or higher). A 2-sided significance level of .05 was set for every analyses.

Results

Baseline Characteristics

Eight hundred and twenty-one patients treated with an SGLT2 inhibitor were matched to 821 control patients. Covariate balance was achieved as emphasized by the final matching specification including a standardized mean difference of −0.0001 (standardized mean difference before matching = 0.3751), a variance ratio of 0.9994 (variance ratio before matching = 0.9869) and a mean empirical cumulative density function (eCDF) of 0.0001 (mean eCDF before matching = 0.0954). Twenty-nine percent of patients (n = 238) were female, and the median (IQR) age was 70 years (61; 78) in each group. Detailed baseline characteristics including comorbidities, medications, and laboratory parameters of each group were well balanced and are shown in Tables 1, 2, and 3.

Prevalence of Hyponatremia on Admission and Association With SGLT2 Inhibitors

Patients treated with SGLT2 inhibitors showed no difference in hyponatremia prevalence on admission compared with the matched control group (9.9%, n = 81 vs 8.9%, n = 73, $P = .554$) (Table 4).

There was no difference in the different hyponatremia severities, specifically, mild (7.9%, n = 65 vs 6.9%, n = 57, $P = .510$), moderate (1.2%, n = 10 vs 1.3%, n = 11, $P = 1.0$), and profound (0.7%, n = 6 vs 0.6%, n = 5, $P = 1.0$), and in hypernatremia prevalence (4.0%, n = 33 vs 5.6%, n = 46, $P = .116$) (Table 4). SGLT2 inhibitors were not associated with hyponatremia (unadjusted odds ratio [OR] 1.12, 95% CI 0.79-1.45, $P = .499$; multivariable adjusted OR 1.08, 95% CI 0.72-1.44, $P = .666$). Furthermore, there was no difference in the median [IQR] plasma sodium concentration between the groups (treated, 140 mmol/L [138-142]; controls, 140 mmol/L [138-142], $P = .1017$) (Fig. 2 and Table 3). SGLT2 inhibitors were not associated with a significant change in plasma sodium levels (unadjusted $\beta = -.08$, 95% CI −0.35-0.51, $P = .712$; multivariable adjusted $\beta = -.24$, 95% CI −0.20-0.68, $P = .280$). Detailed statistical models can be found elsewhere [32].

After excluding patients with an ICD10 code for hypovolemia or hypotension, there was still no difference in hyponatremia prevalence on admission between patients treated with SGLT2 inhibitors and their matched control patients (9.2%, n = 71 vs 9.0%, n = 71, $P = .936$). There was no difference in the different hyponatremia severities, specifically, mild (7.4%, n = 57 vs 7.0%, n = 55, $P = .806$), moderate (1.0%, n = 8 vs 1.4%, n = 11, $P = .687$), and profound (0.8%, n = 6 vs 0.6%, n = 5, $P = .964$), and in hypernatremia prevalence (3.4%, n = 26 vs 5.1%, n = 40, $P = .128$) [32].

Similarly, hyponatremia prevalence was similar in hypervolemic patients treated with an SGLT2 inhibitor and without an SGLT2 inhibitor (13.3%, n = 43 vs 10.7%, n = 37, $P = .363$). There was no difference in the different hyponatremia

Table 1. Demographic characteristics

	No SGLT2 inhibitor on admission (n = 821)	SGLT2 inhibitor on admission (n = 821)
Female, n (%)	238 (29)	238 (29)
Admission year, n (%)		
2015	567 (69.1)	18 (2.2)
2016	129 (15.7)	56 (6.8)
2017	55 (6.7)	124 (15.1)
2018	30 (3.7)	144 (17.5)
2019	24 (2.9)	198 (24.1)
2020	16 (1.9)	281 (34.2)
Age, y, median (IQR)	70.00 (61.00, 78.00)	70.00 (61.00, 78.00)

Demographic characteristics in patients with T2DM treated with an SGLT2 inhibitor and in matched controls with T2DM.

Table 2. Admission diagnoses and comorbidities

	No SGLT2 inhibitor on admission (n = 821)	SGLT2 inhibitor on admission (n = 821)
ICD10 chapter of admission diagnosis, n (%)		
I: Certain infectious and parasitic diseases	52 (6.3)	53 (6.5)
II: Neoplasms	47 (5.7)	48 (5.8)
III: Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	3 (0.4)	2 (0.2)
IV: Endocrine, nutritional and metabolic diseases	50 (6.1)	47 (5.7)
V: Mental and behavioral disorders	6 (0.7)	7 (0.9)
VI: Diseases of the nervous system	29 (3.5)	32 (3.9)
VII: Diseases of the eye and adnexa	3 (0.4)	4 (0.5)
VIII: Diseases of the ear and mastoid process	3 (0.4)	5 (0.6)
IX: Diseases of the circulatory system	258 (31.4)	256 (31.2)
X: Diseases of the respiratory system	95 (11.6)	86 (10.5)
XI: Diseases of the digestive system	57 (6.9)	55 (6.7)
XII: Diseases of the skin and subcutaneous tissue	12 (1.5)	15 (1.8)
XIII: Diseases of the musculoskeletal system and connective tissue	40 (4.9)	40 (4.9)
XIV: Diseases of the genitourinary system	42 (5.1)	44 (5.4)
XVII: Congenital malformations, deformations and chromosomal abnormalities	0 (0.0)	0 (0.0)
XVIII: Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1 (0.1)	1 (0.1)
XIX: Injury, poisoning and certain other consequences of external causes	42 (5.1)	43 (5.2)
XXI: Factors influencing health status and contact with health services	81 (9.9)	82 (10.0)
All diagnoses, n (%)		
Acute kidney injury	45 (5.5)	107 (13.0)
Coronary heart disease	308 (37.5)	399 (48.6)
Acute coronary syndrome	69 (8.4)	91 (11.1)
Chronic kidney disease	262 (31.9)	252 (30.7)
Heart failure	149 (18.1)	149 (18.1)
Hypertension	429 (52.3)	470 (57.2)
Hyponatremia diagnosis	25 (3.0)	29 (3.5)
Hypotension	11 (1.3)	23 (2.8)
Hypovolemia	19 (2.3)	32 (3.9)
Liver cirrhosis	13 (1.6)	16 (1.9)
Lung cancer	16 (1.9)	16 (1.9)
Pneumonia	86 (10.5)	86 (10.5)
Seizure	42 (5.1)	26 (3.2)
Stroke	47 (5.7)	56 (6.8)
Ischemic stroke	43 (5.2)	54 (6.6)
Subarachnoid hemorrhage	1 (0.1)	0 (0.0)
Syndrome of inappropriate antidiuresis (SIAD)	3 (0.4)	2 (0.2)
Tuberculosis	4 (0.5)	3 (0.4)

Admission principal diagnosis as ICD10 chapter and comorbidities in patients with T2DM treated with an SGLT2 inhibitor and in matched controls with T2DM.

severities, specifically, mild (10.8%, n = 35 vs 7.8%, n = 27, $P = .228$), moderate (1.0%, n = 8 vs 1.4%, n = 11, $P = .860$), and profound (0.9%, n = 3 vs 0.9%, n = 3, $P = 1.0$), and in hypernatremia prevalence (5.2%, n = 17 vs 5.8%, n = 20, $P = .894$) [32].

Discussion

The main finding of this cross-sectional study is that hyponatremia prevalence and plasma sodium concentration were the same in patients with T2DM treated with and without SGLT2 inhibitors, irrespective of comorbidities and comedications.

To our knowledge, this is the first study providing data on hyponatremia prevalence in patients with T2DM treated with an SGLT2 inhibitor. Falhammar et al investigated the association between hyponatremia and glucose-lowering drugs; however, the number of patients treated with an SGLT2 inhibitor (n = 2) in their study was too low to investigate their effect on plasma sodium levels [34]. In the current analysis, we chose hyponatremia on admission to investigate the effect of SGLT2 inhibitors because these drugs are commonly paused during hospitalization. Contrary to our hypothesis, we found no difference in the hyponatremia prevalence and plasma sodium levels on admission between patients with T2DM treated with SGLT2 inhibitors and control patients with T2DM without SGLT2 inhibitors. The prevalence of the different hyponatremia severities and of hypernatremia did not differ either.

A first plausible explanation is that we, unfortunately, could not truly differentiate hyponatremia subtypes; in particular, we could not precisely identify hypovolemic hyponatremia, which is one of the most common causes for hyponatremia [35]. A recent meta-analysis by Rong et al suggested that SGLT2 inhibitors are not associated with orthostatic hypotension [36]; however, they reduce blood pressure [37] and induce volume depletion [19]. In hypovolemic hyponatremia, SGLT2 inhibitors might therefore show no effects or even lower plasma sodium levels through hemodynamic AVP stimulation, and thus counterbalance the benefit of SGLT2 inhibitors on plasma sodium levels in euvolemic

Table 3. Medication and laboratory values on admission

	No SGLT2 inhibitor on admission (n = 821)	SGLT2 inhibitor on admission (n = 821)	*P* value
Medication on admission, n (%)			
Antihypertensive agents and diuretics			
ACE inhibitor	191 (23.3)	268 (32.6)	
ARB	172 (21.0)	236 (28.7)	
ARNI	1 (0.1)	32 (3.9)	
Beta blocker	286 (34.8)	406 (49.5)	
Calcium channel antagonists	198 (24.1)	221 (26.9)	
Loop diuretic	222 (27.0)	244 (29.7)	
Mineralocorticoid receptor antagonist	74 (9.0)	110 (13.4)	
Renin inhibitor	6 (0.7)	0 (0.0)	
Thiazide or thiazide-like diuretic	145 (17.7)	183 (22.3)	
Antidiabetic drugs			
Acarbose	0 (0.0)	0 (0.0)	
Biguanide	329 (40.1)	514 (62.6)	
DDP4 inhibitor	189 (23.0)	217 (26.4)	
Glinide	5 (0.6)	4 (0.5)	
GLP-1 receptor agonist	31 (3.8)	100 (12.2)	
Insulin or insulin analog	226 (27.5)	325 (39.6)	
SGLT2 inhibitor	0 (0.0)	821 (100.0)	
Canagliflozin	0 (0.0)	39 (4.8)	
Dapagliflozin	0 (0.0)	184 (22.4)	
Empagliflozin	0 (0.0)	599 (73.0)	
Ertugliflozin	0 (0.0)	0 (0.0)	
Sulfonylurea	77 (9.4)	82 (10.0)	
Thiazolidinedione	5 (0.6)	5 (0.6)	
Antidepressants			
Other antidepressant	5 (0.6)	8 (1.0)	
SNRI	11 (1.3)	13 (1.6)	
SSRI	62 (7.6)	97 (11.8)	
Tetracyclic antidepressant	28 (3.4)	17 (2.1)	
Tricyclic antidepressant	17 (2.1)	15 (1.8)	
Psycholeptics			
Atypical neuroleptics	61 (7.4)	51 (6.2)	
Lithium	8 (1.0)	0 (0.0)	
Typical neuroleptics	16 (1.9)	5 (0.6)	
Anticonvulsants	86 (10.5)	93 (11.3)	
Laboratory values on admission, median (IQR)			
Plasma sodium corrected for glucose (mmol/L)	140 (138, 142), (n = 821)	140 (138, 142), (n = 821)	.1017
Raw plasma sodium (mmol/L)	138 (136, 140), (n = 821)	138 (136, 141), (n = 821)	.2473
Plasma osmolality (mOsm/kg)	300 (290, 317), (n = 23)	296 (287, 314) (n = 26)	.4056
Plasma glucose (mmol/L)	8.8 (6.9, 11.9), (n = 821)	9.1 (7, 12.1), (n = 821)	.2555

Medication and laboratory values on admission in patients with T2DM treated with an SGLT2 inhibitor and in matched controls with T2DM. Raw plasma sodium values and plasma sodium values corrected for glucose are displayed. Plasma sodium values are the first available in the 24 hours following admission. Plasma osmolality and glucose values are from the same samples as plasma sodium values. The 2 groups were compared with a Wilcoxon–Mann–Whitney test.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; GLP, glucagon-like peptide; SGLT2, sodium/glucose cotransporter 2; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors.

and hypervolemic patients in the full dataset. The subgroup analysis we performed was inconclusive: we only extracted ICD10 codes for hypovolemia and hypotension but were not able to account for the other diverse etiologies for hypovolemic hyponatremia (eg, bleeding, third spacing, or gastrointestinal fluid loss) and, therefore, a reliable subset analysis was not possible. In addition, there was no difference in the subgroup of patients with heart failure, liver cirrhosis, or chronic kidney disease as comorbidities. Because we did not perform chart review, we were not able to recognize

Table 4. Prevalence of dysnatremia on admission

	No SGLT2 inhibitor on admission (n = 821)	SGLT2 inhibitor on admission (n = 821)	*P* value
Hypernatremia (plasma sodium >145 mmol/L), n (%)	46 (5.6)	33 (4.0)	.166
Normonatremia (plasma sodium 135–145 mmol/L), n (%)	702 (85.5)	707 (86.1)	.777
Hyponatremia (corrected plasma sodium <135 mmol/L), n (%)	73 (8.9)	81 (9.9)	.554
Mild hyponatremia (plasma sodium 130–134 mmol/L), n (%)	57 (6.9)	65 (7.9)	.510
Moderate hyponatremia (plasma sodium 125–129 mmol/L), n (%)	11 (1.3)	10 (1.2)	1
Profound hyponatremia (plasma sodium <125 mmol/L), n (%)	5 (0.6)	6 (0.7)	1

Prevalence of dysnatremia on admission in patients with T2DM treated with an SGLT2 inhibitor and in matched controls with T2DM (plasma sodium corrected for glucose). The 2 groups were compared with a chi-squared test.

patients with decompensated aforementioned conditions that might have been causative for hyponatremia.

Second, the inhibition of SGLT2 increases glucosuria and natriuresis [38]. One could argue that it would increase urinary sodium clearance and worsen hyponatremia. However, hyponatremia is not a side effect of SGLT2 inhibitors, mainly because the pathophysiology of hyponatremia relies more on a relative water excess than an absolute sodium deficit [39]. Interestingly, our data showed no difference in urine sodium concentration and fractional excretion of sodium between patients with SIAD treated with empagliflozin or a placebo [25, 26]. In patients with T2DM, natriuresis seems to be transient as well [40].

Of note, all patients in this study have T2DM. Even though benefits from SGLT2 inhibitors in heart failure [24, 41] and CKD [42] are irrespective of T2DM, the current findings cannot be extended to patients without T2DM. Glucosuria is more prominent in T2DM [18, 43]; therefore, osmotic diuresis might be greater and favor hypovolemic hyponatremia. Furthermore, we were not able to record treatment duration. Patients with T2DM treated with an SGLT2 inhibitor initially show a reduction of extracellular fluid and an activation of the renin angiotensin aldosterone system, both of which do not persist after 6 months of treatment [44], whereas reduction of extracellular volume persists after 12 weeks in patients with heart failure independently of diabetes [45], which support the hypothesis that the effect of SGLT2 inhibitors might differ in patients with a relative water excess (eg, heart failure, SIAD). In support of this, a recent post hoc analysis of the DAPA-HF placebo-controlled trial investigating the effect of dapagliflozin 10 mg in patients with HFrEF showed a higher prevalence of hyponatremia after 14 days (11.3% vs 9.4%; $P = .04$) but a reduced prevalence of hyponatremia after 12 months (4.6% vs 6.7%; $P = .003$) in the dapagliflozin group [46].

Two of our randomized, double-blind, placebo-controlled trials provided evidence that empagliflozin is an effective treatment: first, in hospitalized patients with SIAD [25], and, second, in outpatients with chronic SIAD [26]. Furthermore, a

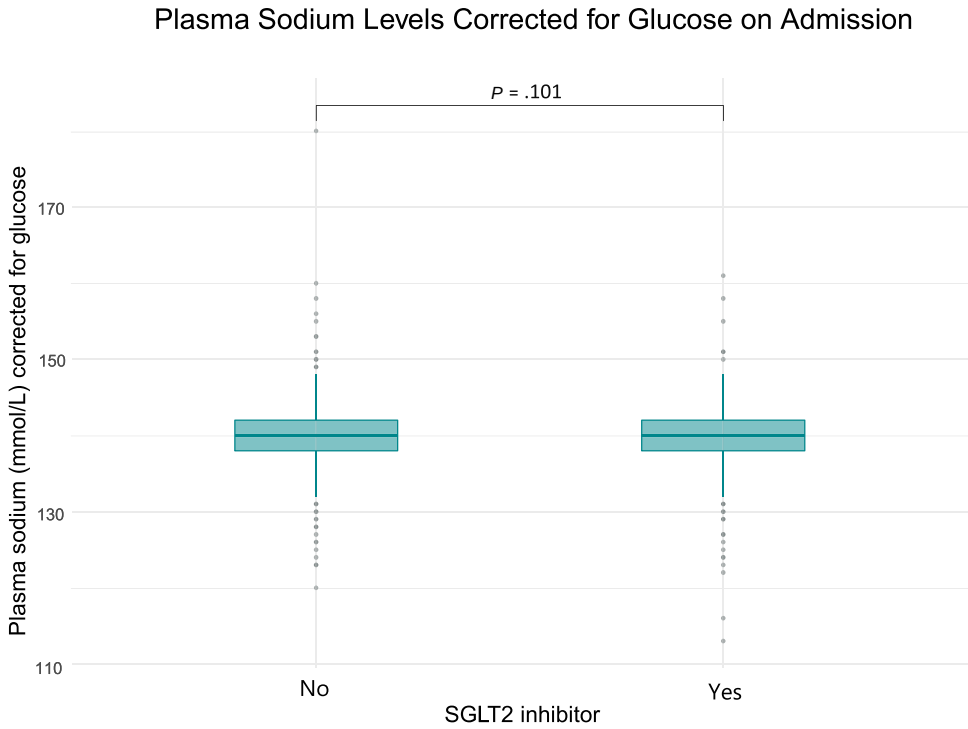

Figure 2. Plasma sodium levels on admission. Plasma sodium levels in mmol/L for each group: patients with diabetes treated with an SGLT2 inhibitor (n = 821) and matched controls (n = 774). Boxes span the interquartile range (IQR); the thick horizontal line is the median. Whiskers are the most extreme values lying within the box edge and 1.5 times the IQR. All other values are considered to be outliers and plotted as individual points. A Wilcoxon–Mann–Whitney test was performed to compare hyponatremia levels in both groups.

post hoc analysis in patients with HFrEF [46] and case reports in patients with liver cirrhosis [47] suggests that SGLT2 inhibitors might represent an effective option for these hyponatremic subgroups. Long-term SGLT2 inhibitor treatment might only influence plasma sodium levels in patients with overt euvolemic or hypervolemic hyponatremia, in other words, with a relative body water excess. The effect of SGLT2 inhibitors in hypervolemic hyponatremic patients with heart failure or liver cirrhosis is currently being investigated in a multicentric, randomized, double-blind, placebo-controlled trial (NCT04447911).

Finally, cross-sectional studies provide helpful insight into associations but yield poor information about causal relationships. Therefore, findings should be cautiously interpreted [48]. The incongruence between our retrospective observational results and our prospective randomized data [25, 26] underlines this limitation.

Conclusion

Based on this cross-sectional retrospective study, SGLT2 inhibitors do not prevent hyponatremia development. These findings do not support their use as hyponatremia prophylaxis in at-risk patients. Prospective randomized data suggest their efficacy at a higher dosage in overt SIAD [25, 26], but their efficacy in other hyponatremia subtypes remains to be demonstrated. An ongoing randomized, placebo-controlled study will help better define the role of empagliflozin in overt euvolemic and hypervolemic hyponatremia (NCT04447911).

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Author Contributions

S.M. conceived, designed, and performed the analysis and wrote the first draft of the manuscript. C.A. and J.R. reviewed the manuscript. M.C.C. revised the manuscript and supervised all steps of the work.

Disclosures

S.M., C.A., J.R., and M.C.C. have nothing to disclose.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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