Primary polydipsia in the medical and psychiatric patients

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Summary of the project

Background: Primary polydipsia is characterized by increased fluid intake and consistent excretion of profound quantities of diluted urine. It has mainly been described in psychiatric patients but with the current lifestyle-trend and believe that fluid intake is healthy, it is speculated to be increasing in the general population. One of the main and most severe complications of primary polydipsia is hyponatremia, which occurs when free water intake exceeds free water excretion. Despite the increasing prevalence, consistent clinical data on patients with primary polydipsia is lacking. Most of the existing data stems from case reports and retrospective studies within the psychiatric setting, particularly from patients with a schizophrenia spectrum disorder. Pathophysiological understanding and the risk for hyponatremia in non-psychiatric patients remains unclear. Treatment options for patients with primary polydipsia are scarce and have mainly been studied in the psychiatric setting.

Objective: This MD-PhD thesis aims at contributing to improving the pathophysiological understanding of, to characterize complications in, and to find treatment options for patients with primary polydipsia.

Methods: To reach the aspired aim, I first performed a secondary analysis of a prospective observational study to characterize patients with primary polydipsia hospitalized with profound hyponatremia. Second, I investigated the association of hyponatremia and outdoor temperature in patients with and without primary polydipsia in three distinct cohorts. Third, I was involved in a randomized, placebo-controlled cross-over trial evaluating glucagon-like peptide-1 receptor agonists, medications used to treat type 2 diabetes mellitus and obesity, as a treatment option for patients with primary polydipsia.

Results: First, primary polydipsia's main complication, i.e. hyponatremia, also occurs in medical patients also without psychiatric comorbidities. Second, the risk of profound hyponatremia increases in all polydisic patients in the presence of contributing factors impairing the renal excretory capacity: low solute intake or increased arginine vasopressin. Primary polydipsia in association with profound hyponatremia is furthermore associated with a poor outcome, e.g. hyponatremia recurrence, rehospitalization, and death. Third, hyponatremia shows a season dependent effect with increased hyponatremia prevalence during summer months in correlation with increased outdoor temperature. Fourth, glucagon-like peptide-1 receptor agonists reduce fluid intake in patients with primary polydipsia.

Conclusion: Primary polydipsia has mainly been described in the psychiatric setting, but it seems to be also common in the general population. Special attention should be paid in patients with primary polydipsia to reduce hyponatremia inducing factors and prevent hyponatremia. Glucagon-like peptide-1 receptor agonists are a promising new treatment option for patients with primary polydipsia.

Acknowledgments

This dissertation would have never been possible without the committed support of my supervisor, colleagues, family, and friends. My deepest gratitude is expressed towards my supervisor and mentor, Professor Mirjam Christ-Crain, who supported me professionally and privately throughout the whole time of my MD-PhD. She not only gave me the unique opportunity to participate in different observational and interventional studies, but she also trusted me to initiate clinical trials based on my own research ideas. Her commitment for scientific research, more specifically, her engagement in supporting young and motivated physicians and clinical researchers is inspiring. Mirjam found time whenever I was in doubt and needed someone to encourage me to continue with my work. She supported my enthusiasm for new research ideas and helped me to successfully publish my research in renowned endocrine journals. Each published paper and received award were celebrated in her team, fostering a positive and productive work environment. It was my greatest pleasure to work in Mirjam's research team and have her as my mentor and friend. I will forever be grateful for her trust in me as her first MD-PhD student in clinical research.

I would also like to thank Professor Stefan Borgwardt for his support throughout my MD-PhD and for the collaboration he enabled with the psychiatric department. His expertise and different view were highly valuable throughout my research.

From my first day as a MD-PhD student I was fortunate to be surrounded by excellent clinical researchers and physicians, who supported me in achieving my goals. Particularly, I would like to thank Dr Bettina Winzeler who helped analyze the data and writing of my first manuscripts. Her constant feedback and critical revision honed important skills required in clinical research. Furthermore, I would like to thank Dr Julie Refardt who inspired me to be persistent, who supported me in difficult times, and who was the first to celebrate success.

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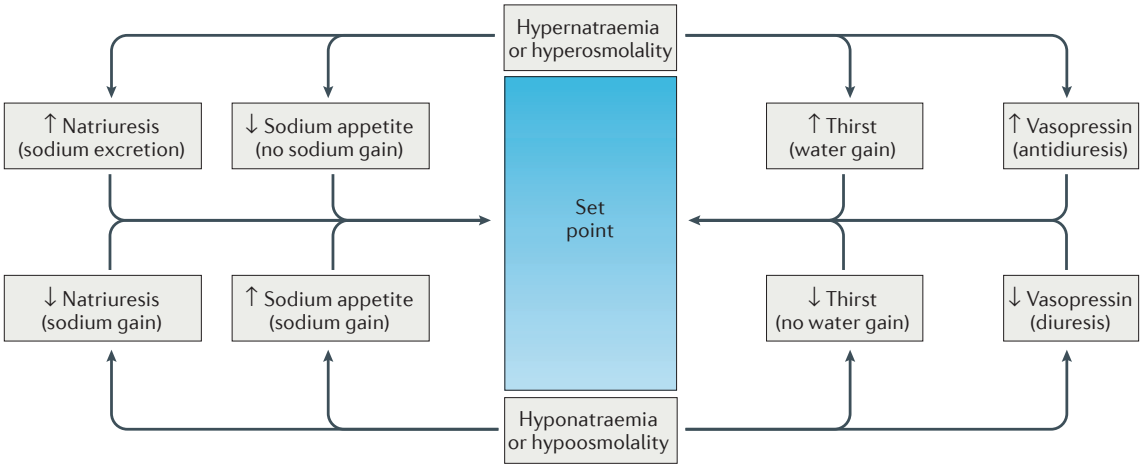
Introduction

Primary polydipsia is characterized by increased fluid consumption (>3000 ml/day) and consistent excretion of profound quantities of diluted urine (>40-50 ml/kg body weight per day) over an extended period of time, excluding reasons for secondary polydipsia, e.g. hyperglycemia, hypercalcemia [1–3]. It has most commonly been described in neurodevelopmental disorders, such as autism and intellectual disability, or psychotic disorders, such as schizophrenia spectrum, schizoaffective, bipolar disorder, and psychotic depression [1,3,4]. A particularly high prevalence in primary polydipsia has been described in chronic schizophrenia with a prevalence of 11–20% of patients [4,5]. With the increasing popularity of lifestyle-trends proclaiming that consuming plenty of fluid per day is healthy, is detoxifying, and improves cognition, the prevalence of this phenomenon seems to be constantly increasing, particularly outside of the psychiatric setting. Nevertheless, the prevalence of primary polydipsia in the general population and the current prevalence in the psychiatric setting is unknown. Presumably, a lack of knowledge regarding the burden of, consequences of, and treatment options for this disorder has limited studies in this field until now.

Pathophysiology of primary polydipsia

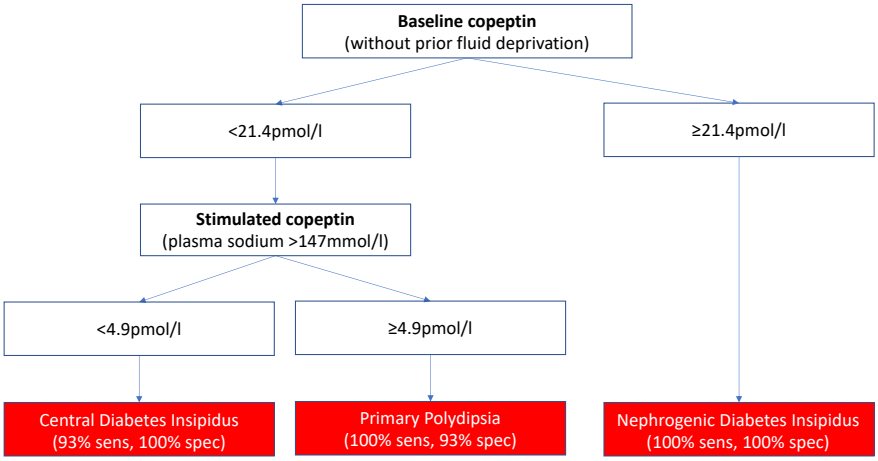
Maintaining a stable fluid level is a primary human need [6,7]. Water balance is an incessant equilibrium of water intake and its excretion through the kidneys, lungs, bowels, and skin. This balance, in order to keep plasma osmolality within a close range, is primarily regulated by the interplay of thirst and the hormone arginine vasopressin [8]. Arginine vasopressin, promoting water retention in the kidney, is released upon two main stimuli: high serum osmolality and low arterial blood volume [6,8–10]. At the same time, a stimulus induces thirst perception leads to water intake. In primary polydipsia, arginine vasopressin levels are physiologically suppressed to compensate for the low serum osmolality following the increased fluid intake.



In healthy people, drinking leads to a pleasant feeling in response to thirst with an activation of the prefrontal cortex, the pleasure and reward center of the brain, as shown in neuroimaging experiments. In contrast, increased drinking after thirst has been satisfied, results in an unpleasant or even aversive sensation, which then stops the healthy person from further fluid intake [11,12]. Some patients with primary polydipsia report a drop of thirst after consuming water followed by a sudden rebound [4]. A dysfunction in the thirst center has been discussed as a pathophysiological process in patients with primary polydipsia, as described in patients with sarcoidosis [13]. It is speculated that some patients with primary polydipsia experience increased thirst in response to a lower osmotic set point for arginine vasopressin release [14]. Nevertheless, the pathogenesis of altered thirst and excessive fluid intake as seen in patients with primary polydipsia remains largely unknown.

Differential diagnosis of the polyuria-polydipsia syndrome

Primary polydipsia belongs to the polyuria-polydipsia syndrome. The differential diagnoses of primary polydipsia are central and nephrogenic diabetes insipidus. While primary polydipsia is primarily characterized by increased fluid intake, diabetes insipidus is determined by polyuria due to impaired arginine vasopressin secretion (central diabetes insipidus) or arginine vasopressin resistance in the kidneys (nephrogenic diabetes insipidus) with consecutive polydipsia to replace the lost fluid [9]. Until recently, the widely accepted gold standard for the differential diagnosis of the polyuria-polydipsia syndrome was the indirect water deprivation test, introduced in 1970 [15,16]. However, this procedure is limited by a poor diagnostic accuracy: 70% overall and only 41% for primary polydipsia [17]. Other methods have been studied, including direct measurement of vasopressin and of the vasopressin surrogate marker copeptin [3,18,19]. A baseline measurement of copeptin can differentiate between nephrogenic diabetes insipidus and central diabetes insipidus or primary polydipsia [19]. Currently, the most reliable method to differentiate between primary polydipsia and central diabetes insipidus is a stimulated copeptin level following hypertonic saline infusion [17]. This test, importantly, requires constant supervision by a trained physician due to side effects and the risk of sodium overstimulation. Arginine is known to stimulate prolactin and growth hormone from the anterior pituitary [20,21]. As arginine is well tolerated, it is widely used as provocation test to diagnose growth hormone deficiency, especially in children [22]. In accordance with the effects of other growth hormone secretagogues (e.g., hexarelin) [23,24], arginine could also stimulate the posterior pituitary (i.e., to release vasopressin) and might therefore provide a simple, alternative diagnostic test in the differential diagnosis of diabetes insipidus.



Complications of primary polydipsia

One of the most common and severe acute complication of primary polydipsia is the development of hyponatremia [5,25,26]. Hyponatremia in patients with primary polydipsia occurs when free fluid intake exceeds free fluid excretion [25,27,28]. It is often associated with psychotic exacerbation of chronic schizophrenia [29]. The normal excretory capacity of the kidneys can compensate for fluid intake up to 15-18 l/day (considering a maximum urine diluting capacity of 50 mmol/l and an excretion of 900 mmol/24h), but this system may be disturbed by factors influencing the water excretion such as medications, stress, or low sodium intake [27].

Most of the research on complications, especially hyponatremia, has been done in patients with chronic schizophrenia, where a hyponatremia prevalence of up to 20% in patients with psychogenic polydipsia has been found [5,30,31]. Information on the prevalence of hyponatremia in medical patients with primary polydipsia is scarce. Additionally, precipitating factors for hyponatremia and outcome have been poorly studied for patients with primary polydipsia.

Treatment options for patients with primary polydipsia

Voluntary reduction of water intake would be the ideal treatment for patients with primary polydipsia but often fails due to non-compliance of the polydiptic patient who suffers from thirst and compulsive drinking behavior [29,32,33]. Studies investigating behavioral therapy, such as disease education, relaxation training using biofeedback, conditioning of desired behavior, and group therapy, have shown to be the most success [34–37]. However, the feasibility of behavioral therapy, requiring substantial time and manpower, are limited in an outpatient setting [34]. Different medications have been suggested to improve polydiptic behavior and prevent hyponatremia. Most drugs showing symptom improvement are antipsychotic drugs and mood stabilizers, such as olanzapine, lithium, risperidone, aripiprazole, and clozapine [38–43]. The question however remains whether these drugs are treating the urge to drink, or whether they simply reduce acute psychosis and thereby treat

primary polydipsia that might be a symptom of acute psychosis. Other medications have been studied in and outside the psychiatric setting with limited success to reduce polydiptic behavior: phenytoin, bupropion, and propranolol [44,45]. In conclusion, treatment options for patients with primary polydipsia, especially outside the psychiatric setting, are scarce.

Importance and impact

Primary polydipsia has mainly been described in the psychiatric setting. Outside the psychiatric setting, it has been described in young to middle aged life-style conscious people who feel the need to detoxicate their body and consider plenty of fluid intake healthy. Nevertheless, primary polydipsia bears the risk of complications, mainly hyponatremia, which is associated with morbidity, mortality, and health service utilization [31,46].

Consistent clinical data on patients with primary polydipsia is lacking. Most of the existing data arises from case reports and retrospective studies within the psychiatric setting, and especially from patients with a schizophrenia spectrum disorder. Pathophysiological understanding and the risk for hyponatremia in non-psychiatric patients remains unclear. Furthermore, current treatment options are scarce and have mainly been studied in the psychiatric setting.

This indicates the need for further research in the field of primary polydipsia with the focus on improving the pathophysiological understanding of primary polydipsia, characterizing complications in non-psychiatric patients, and finding treatment options that are safe and efficient for medical and psychiatric patients with primary polydipsia.

Main objectives of this MD-PhD

This MD-PhD thesis aims at improving the pathophysiological understanding of, to characterize complications in, and to find treatment options for patients with primary polydipsia.
In the following, the different objectives and methodologies to accomplish these aims are described.

Objective 1: Prevalence and pathophysiology of primary polydipsia

Part 1 (prevalence): To clarify the current prevalence of, characterize, and investigate the outcome of patients with primary polydipsia in the acute psychotic patient, I planned, organized, and conducted a prospective observational study with a one-year follow-up.
Part 2: (pathophysiology): To improve the pathophysiological understanding of patients with primary polydipsia, I designed, planned, and performed a neuroimaging study in patients with primary polydipsia and healthy volunteers.

Objective 2: Differential diagnosis of the polyuria-polydipsia syndrome

To improve differential diagnosis in patients with polyuria-polydipsia, I participated in a diagnostic study investigating copeptin levels following arginine infusion test as an alternative to the hypertonic saline infusion test.

Objective 3: Complications of primary polydipsia

Part 1: To investigate, characterize, and describe complications of patients with primary polydipsia, I performed a secondary analysis of a prospective observational study including a one-year follow up of patients hospitalized with profound hyponatremia due to primary polydipsia.
Part 2: To clarify a season dependent effect of hyponatremia in patients with primary polydipsia, I investigated three different medical cohorts with hyponatremia in correlation to outdoor temperature with and without primary polydipsia.

Objective 4: Treatment options for patients with primary polydipsia

To investigate a new treatment option for patients with primary polydipsia, I participated in a randomized, placebo-controlled cross-over trial in patients with primary polydipsia receiving glucagon-like peptide-1 receptor agonists.

Contribution by the MD-PhD student

I had the great honor to be part of Professor Mirjam Christ-Crain's research group for the whole time of my MD-PhD in clinical research. I was involved in several projects within the field of primary polydipsia and hyponatremia. I learned all relevant steps of clinical research from the planning of the project, the writing of the ethical and funding proposal, to the conduction of the project, the analysis and interpretation of the data, and the writing of the manuscript.

At the beginning of my MD-PhD, I performed a thorough literature research and wrote a narrative review on characteristics, differential diagnosis, complications, and treatment options of patients with primary polydipsia [47]. During the literature research and the writing of the review, I identified several gaps in the field of primary polydipsia: first, uncertainty about the pathophysiology of primary polydipsia; second, a lack in prevalence of complications, mainly hyponatremia, in the medical patient with primary polydipsia; third, lack of an easy and accurate test for the differential diagnosis of the polyuria-polydipsia syndrome; fourth insufficient treatment options for patients with primary polydipsia.

To shed light on these uncertainties, I analyzed data of a prospective observational study and wrote my first original paper on characteristics and outcome of patients with primary polydipsia and hyponatremia [48]. I was able to perform this analysis thanks to my knowledge from several statistical courses and was furthermore supported by the Clinical Trial Unit in Basel. I discussed and interpreted the data and wrote the manuscript with the support from Dr Bettina Winzeler and Professor Mirjam Christ-Crain.

To clarify a season dependent effect of hyponatremia in patients with and without hyponatremia, I combined three data sets: first, the results from a prospective observational study, second, chart data from the emergency department, and third, meteorological data (temperature and humidity). Again, I analyzed the data, discussed the results and wrote the manuscript with the support dem the Clinical Trial Unit Basel, Dr Bettina Winzeler, and Professor Mirjam Christ-Crain [49]. To confirm the findings, I performed a similar analysis in a nation-wide cohort study together with Dr Alexander Kutz and Dr Fahim Ebrahimi [50].

To further investigate the prevalence of primary polydipsia in the psychiatric setting, I designed a prospective observational study in patients with an acute psychosis, where primary polydipsia has mainly been described (CoPsych Trial, NCT03235908). I planned the study, initiated the collaboration with the psychiatry department with Professor Stefan Borgwardt and Jennifer Küster, wrote the ethical proposal, and performed the patients' visits. I finished recruitment of this study in July 2019 after including 73 patients and will continue with the one-year follow-up until July 2020. Thereafter, I will analyze the data and write the manuscript in collaboration with Professor Stefan Borgwardt and Jennifer Küster.

I was also involved in a study investigating the differential diagnosis of the polyuria-polydipsia syndrome. This study showed that copeptin measurement after arginine infusion can differentiate between patients with primary polydipsia and central diabetes insipidus [51].

I was co-investigator of a randomized controlled trial investigating glucagon-like peptide 1 (GLP-1) receptor agonists as a potential treatment option for patients with primary polydipsia (GOLD-trial, NCT02770885). After finishing the recruitment, I am currently writing the manuscript with the help of Dr Bettina Winzeler and Professor Mirjam Christ-Crain. As part of the study, I initiated a sub-study in 15 patients with primary polydipsia and 15 healthy matched controls to investigate neuronal changes using a functional magnet resonance imaging. Here, I wrote the amendment, coordinated the study set up with the radiology department, and set up the paradigm. I recruited patients and controls and performed patients' visit. Recruitment ended in summer 2019 and I am currently analyzing the functional magnet resonance images using the software package FMRIB Software Library (FSL).

Furthermore, I was the principle investigator in a randomized cross-over study investigating the influence of alcohol consumption with and without additional fluid and sodium on copeptin levels in ten healthy men. Here, I designed and planned the trial, drafted the ethical proposal, recruited patients, and performed patients' visits. After the data analysis, I wrote the manuscript [52]. As part of this project, I supervised a master student and gained valuable leadership skills.

Additionally, I recruited and performed regular study visits in a randomized, placebo-controlled trial investigating empagliflozin as treatment option for patients with the syndrome of inappropriate antidiuresis [53]. I presented this study at the local scientific meeting and was awarded with the second price for the oral presentation.

Overall, I have gained many valuable skills during my MD-PhD that are necessary for clinical research. I was involved from the beginning of a new research project to the presentation of the data and writing of the manuscript. I learned basic and advanced statistical skills as well as leadership, teambuilding, and communication skills.

Review: Primary polydipsia in the medical and psychiatric patient: characteristics, complications and therapy

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Abstract

Primary polydipsia (PP) has been defined as excessive intake of fluids. However, the pathogenesis of PP remains unexplored. Different theories include a dysfunction in the thirst mechanism, involvement of the hippocampus, stress-reducing behaviour and lesion occurrences in specific areas of the brain. Most studies have been performed in the psychiatric setting, indicating that PP coincides with schizophrenia, anxiety disorder and depression. However, an increasing number of case reports emphasise the incidence of PP in non-psychiatric patients. As often recommended by healthcare professions and in life-style programmes, the phenomenon of excessive fluid intake appears to be growing, especially in health-conscious and active people. PP is part of the polyuria-polydipsia syndrome, so the differential diagnosis diabetes insipidus (central or nephrogenic) must be excluded. The gold standard when differentiating between these disorders has been the water deprivation test. However, new options for distinguishing between these entities have been proposed e.g., measurement of copeptin, a reliable surrogate marker of the hormone arginine vasopressin (AVP). The major risk of excessive drinking is the development of hyponatraemia and the ensuing complications. In patients with PP, factors reducing the renal excretory capacity of the kidney such as acute illness, medications or low solute intake may accumulate in hyponatraemia. Treatment options for PP remain scarce. Different medication and behavioural therapy have been investigated, but never on a large scale and rarely in non-psychiatric patients. This review provides an overview of the pathophysiology, characteristics, complications, and outcomes of patients with PP in the medical and psychiatric patient.

Introduction

Primary polydipsia (PP) is characterised by an increased fluid intake and consistent excretion of profound quantities

of dilute urine exceeding 40–50 ml/kg body weight (e.g., 3000 ml/day for a person of 60 kg) over an extended period, excluding reasons for secondary polydipsia [1–3]. It has most commonly been described in patients with schizophrenia spectrum disorder with an incidence of 11 to 20%, and has therefore been named psychogenic polydipsia [1–3,5]. With the increasing popularity of lifestyle programmes and the common conception that consuming several litres of fluid per day is healthy, the prevalence of this phenomenon is increasing, particularly outside of the psychiatric setting. However, the prevalence in the overall population is unknown and has yet to be studied. Presumably, a lack of knowledge regarding the burden, consequences and treatment options for this disorder has limited studies in this field until now.

A comparable disorder is beer potomania, which is also characterised by increased intake of beer, but in this condition urine output may be below the above-mentioned polyuria definition [54–57].

The most common and potentially severe complication of excessive fluid intake is the occurrence of hyponatraemia [1,5,26,30]. Hyponatraemia is associated with increased morbidity and mortality and should therefore be prevented [31,46,58,59]. Different risk factors are thought to be associated with the development of hyponatraemia in PP such as medication, physical or psychological stress, and acute consumption of copious quantities of fluids [1,5,30].

Several treatment options for PP have been investigated, ranging from different medication to behavioural therapy [36–39,60,61]. Unfortunately, most studies were using explorative study designs, small sample sizes with limited success, and low generalisability.

This review is intended to give an overview of the current stage of research in the field of PP. We will describe causes, associated comorbidities, complications, and will discuss the diagnostic and therapeutic issues of this syndrome.

Pathophysiology

Maintaining a stable fluid level is a primary human need [6,7]. Water balance is an incessant equilibrium of water intake and excretion through the kidneys, the lungs, the bowels and the skin. This balance, in order to keep plasma osmolality within a close range, is primarily regulated by the interplay of thirst and the hormone arginine vasopressin (AVP)[8]. AVP, promoting water retention in the kidney, is released upon two main stimuli namely high serum osmolality and low arterial blood volume [6,8,9] (fig. 1).

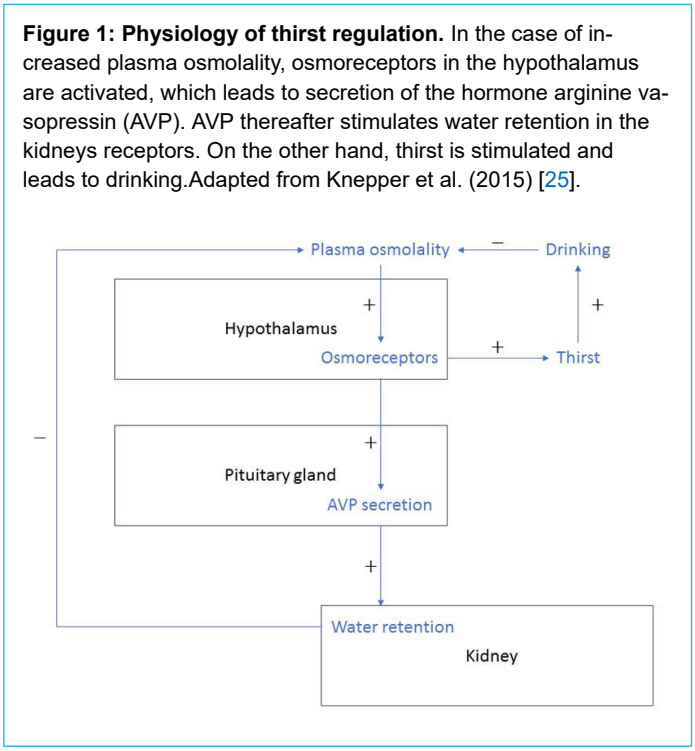


Figure 1: Physiology of thirst regulation. In the case of increased plasma osmolality, osmoreceptors in the hypothalamus are activated, which leads to secretion of the hormone arginine vasopressin (AVP). AVP thereafter stimulates water retention in the kidneys receptors. On the other hand, thirst is stimulated and leads to drinking.Adapted from Knepper et al. (2015) [25].

In healthy people, drinking leads to a pleasant feeling in response to thirst with an activation of the prefrontal cortex, the pleasure and reward centre of the brain, as shown in functional magnet resonance imaging (fMRI) experiments. In contrast, increased drinking after thirst has been satisfied results in an unpleasant or even aversive sensation, which then stops the healthy participant from further fluid intake [11,12].

The pathogenesis of insatiable thirst and excessive fluid intake as seen in PP remains largely unknown. According to the underlying or associated conditions, PP may be classified in two main categories, whereby different causal mechanisms are discussed: psychogenic polydipsia and dipsogenic polydipsia [2,9,19,48] (table 1). A related disorder is beer potomania, which is characterised by the chronic or acute consumption of large amounts of beer [56,62].

Table 1 Causes of primary polydipsia			
Primary Polydipsia (excessive water intake)			
	Psychogenic Polydipsia (e.g. in patients with acute psychosis, chronic schizophrenia spectrum disorder, anxiety disorder, depression, anorexia nervosa and dependency disorder)		
	Dipsogenic Polydipsia		
		Habitual polydipsia	
			Health conscious men and women
			Athletics
		Somatic (damage of thirst centre)	
			Cerebral lesion
			Granulomatous (sarcoidosis)
			Infectious (tuberculous meningitis)
			Vascular (vasculitis)
	Beer potomania (excessive beer intake)		

Most research has been done in patients with schizophrenia spectrum disorders and psychogenic polydipsia. In both, a central defect of thirst and a dysfunction in AVP regulation has been suggested [25,63]. During acute psychotic episodes, worsening of polydiptic behaviour and increased levels of AVP have been observed [30]. It is speculated that during acute psychosis, the activation of the hypothalamic-pituitary-adrenal axis and AVP secretion influences behavioural traits and vice versa – probably through hippocampal involvement [8,30,64–68]. Interestingly, in cranial MRI, the hippocampus was found to have a diminished volume in patients with schizophrenia spectrum disorder and PP compared to those without PP [66].

Furthermore, a stress-induced increase in dopamine levels may also play a role in acute psychotic patients. This hypothesis has been tested in animal studies, which showed that exogenous dopamine initiated drinking and increased AVP levels [69–72].

Other psychiatric conditions such as affective and dependency disorder (e.g., smoking, alcoholism) and anorexia nervosa also appear frequently in PP [48]. In these diseases, drinking might be perceived as a coping strategy to deal with psychological stress or, especially in patients with anorexia nervosa, increased fluid intake may compensate for low food intake and to decrease the sensation of hunger [63,73,74].

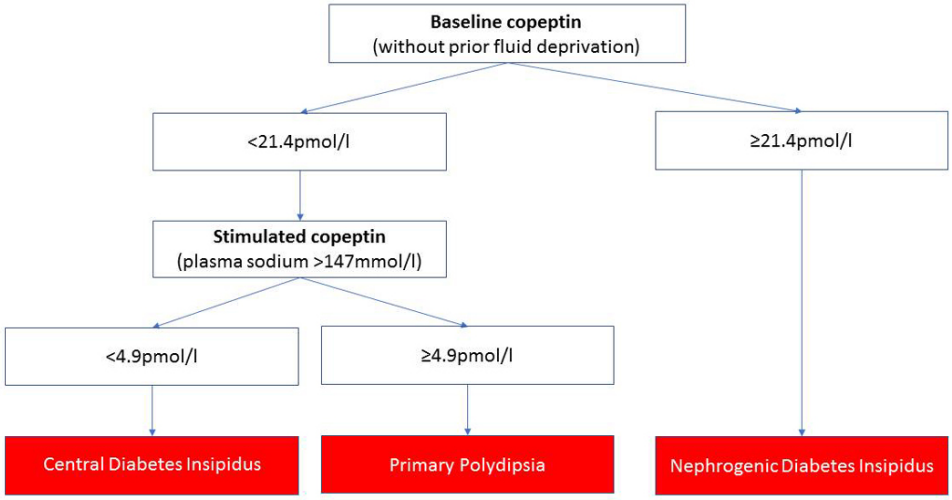
Dipsogenic polydipsia includes patients with an increased sensation of thirst due to hypothalamic lesions and subjects with habitual polydipsia, which is typically seen in lifestyle conscious men and women, which is the use of water to detox the body. Abnormally high water consumption is also seen

in people who perform excessive amounts of sport [75–79]. Alongside hypothalamic affection after traumatic brain injuries, vascular or infiltrative diseases (e.g., sarcoidosis) may lead to dipsogenic polydipsia [9,13,80–82]. In habitual polydipsia, social conditioning with constant motivation to drink may modify drinking behaviour relative to actual water deficit, thus resulting in a downward resetting of the thirst threshold[11,12]. Finally, while in beer potomania the underlying disorder is alcohol dependency, the motivation to drink is the effect of alcohol and thus different from other forms of primary polydipsia[54–57]. Psychogenic and dipsogenic polydipsia seem to occur preferentially in women, whereas beer potomania is more often seen in men [1,5,31,48].

Diagnosis and differential diagnosis of PP

The differential diagnoses of primary polydipsia (PP) are central and nephrogenic diabetes insipidus (DI). While PP is primarily characterised by increased fluid intake, DI is determined by polyuria due to impaired AVP secretion (central DI) or AVP resistance in the kidneys (nephrogenic DI) [9]. Central DI may be acquired after e.g., pituitary trauma (surgery), infections, auto-immune disease or congenital factors [2,3,9,83]. Nephrogenic DI can be due to inherited mutations in the AVP-receptor-2 and aquaporine-2 gene, or acquired (e.g., chronic lithium use or metabolic/vascular kidney injuries) [3,83].
The first step in the diagnosis and differential diagnosis of PP is a thorough history, including medical and psychiatric comorbidities and medication. Compared to patients with DI, polydiptic patients typically report a less acute onset and often deny nocturia and drinking during the night [9]. The next diagnostic step is to exclude other forms of polyuria (e.g., diabetes mellitus) and to measure plasma, urine osmolality and electrolytes. Low normal plasma sodium in the presence of a low urine osmolality is indicative of PP. The widely accepted gold standard for the differential diagnosis of PP is the indirect water deprivation test, introduced in 1964 [15]. The test indirectly assesses AVP activity by measurement of urinary osmolality, and thus the concentration capacity of the kidneys, during a prolonged dehydration period, and finishes by assessing the response (increase in urinary osmolality in %) to the administration of exogenous vasopressin (desmopressin) [84–86].
However, this procedure is limited by poor diagnostic accuracy of 70% overall and an especially poor diagnostic performance of only 41% for PP [2,87]. Therefore, other methods have been studied. Direct measurement of AVP was used with initially promising results [18]. However, due to measuring difficulties and the instability of AVP, direct measurement of AVP has never entered everyday practice [28,88,89].
Copeptin, the c-terminal part of the AVP precursor peptide, was found to be a stable, sensitive and easily measured surrogate marker for AVP [88,90,91]. Copeptin has been shown to accurately discriminate between PP and DI [91,92]. Without prior thirsting, a single basal copeptin value >21.4 pmol/l differentiates nephrogenic DI from other aetiologies with a high sensitivity and specificity. If the basal copeptin value is below this cut-off, an osmotic stimulation (plasma sodium >147 mmol/l) either by fluid restriction or the administration of a hypertonic saline infusion is necessary for differentiation between central DI and PP [92]. An osmotically stimulated copeptin value ≥4.9 pmol/l differentiates between patients with PP and central DI with high diagnostic accuracy (fig. 2).

Figure 2: Diagnostic algorithm of copeptin in the differential diagnosis of patients with PP, central and nephrogenic DI. A basal copeptin value of ≥21.4 pmol/l confirms the diagnosis of nephrogenic DI. A basal copeptin value of <21.4 pmol/l needs an osmotic stimulation (water deprivation or hypertonic saline infusion) to differentiate between central DI and PP. An osmotically stimulated copeptin value ≥4.9 pmol/l differentiates between patients with central DI and PP with a high diagnostic accuracy [28].Adapted from Christ-Crain and Fenske (2016) [53].



Complications of PP

The most common and severe acute complication of PP is the development of hyponatraemia [26,31,62,93]. Hyponatraemia in PP occurs when free fluid intake exceeds free fluid excretion [25,27,28]. The normal excretory capacity of the kidneys can compensate for liquid intake up to 15-18l/day (considering a maximum urine diluting capacity of 50mmol/l and an excretion of 900mmol/24h), but this system may be altered by several factors [27]. Beside chronic and acute ingestion of excessive quantities of fluids, conditions impairing urine dilution capacity predispose hyponatraemia - primarily increased AVP release [1,25–27,31,93–98]. Risk factors for hyponatraemia are displayed in table 2.

Table 2 Factors predisposing hyponatremia in primary polydipsia	
Acute fluid intake of high amount	
Impaired water excretion	
	Low solute intake
	Malnutrition
	Anorexia nervosa
	Beer potomania
	Concomitant AVP stimulus
	Medication (e.g. antidepressants, antipsychotics, diuretics)
	Acute infection (e.g. pneumonia, urogenital tract infection) or other acute diseases (e.g. stroke, myocardial infarction)
	Psychological stress (e.g. acute psychosis)

About 20% of patients with schizophrenia and PP develop hyponatraemia [5,30,31]. As AVP is known to be a stress hormone, an acute psychotic episode increases the activity of AVP, leading to water retention and potentially hyponatraemia, especially if polydiptic behaviour persists [28,30,99]. Similarly, somatic stress (e.g., acute diseases, pain) stimulates AVP secretion [100]. Recent case reports have shown an association between acute infection and hyponatraemia. Particularly in urinary tract infections when both the infection per se and stress-induced AVP release reduce the renal excretory capacity, a combined with medical advice to increase fluid intake, patients in general and especially with PP are at risk of the development of hyponatraemia [101–104].

Several medications may promote hyponatraemia by stimulating AVP release or increasing the sensitivity of the kidneys to AVP: thiazide diuretics, antipsychotic drugs, antidepressant drugs, antiepileptic drugs, and lithium [94,96,98,105–108]. Furthermore, the anticholinergic side effects of antidepressant drugs may result in an elevated sensation of thirst and hence lead to increased drinking.

In patients with beer potomania, patients with PP and malnutrition or anorexia nervosa, low solute intake plays a major role in the development of hyponatraemia [62]. The amount of solute intake defines the maximum dilution capacity of the kidneys as free fluid without solutes cannot be excreted. Thus, if solute intake decreases, the kidneys' excretory capacity of water may decrease from around 15 l/d to 4 l/d, a threshold that is quickly passed in patients with chronic polydipsia and beer potomania [27]. Hyponatraemia may lead to several serious consequences. In the acute setting, if hyponatraemia treatment is delayed or inadequate, complications include brain oedema, seizures, falls and fractures as well as rhabdomyolysis and central pontine myelinolysis [31,109–113]. In the long-term, hyponatraemia is associated with increased rehospitalisation rates, morbidity and mortality [58,114]. Importantly, the risk of hyponatraemia seems to increase with duration of the underlying disease of PP[5]. It is speculated that excessive fluid intake over a long period may modulate drinking behaviour relative to actual water deficit and lead to a disturbance in the osmoregulation. Hence, over time, subjects declare thirst and keep drinking even in the presence of reduced serum osmolality [28,32,115]. Similarly, a downward resetting of the osmostat results in delayed or incomplete suppression of AVP and hence impairs water excretion.

Beside hyponatraemia, other complications of chronic excessive fluid consumption exist. Renal concentration capacity may diminish through a washout mechanism and downregulation of aquaporine-2 water channels, as shown in rodents [116]. Furthermore, malnutrition, gastrointestinal distress, bladder dilatation, hydronephrosis, renal failure, congestive heart failure, osteopenia and central nervous system dysfunction have been discussed [35,37,46,117]. These data, however, mostly derive from case reports and retrospective studies and therefore provide low evidence.

Treating primary polydipsia and its complications

Treatment options for PP are scarce. Voluntary reduction of water intake would be the ideal therapy for PP, however, it often fails due to non-compliance of the polydiptic patient who suffers from thirst and compulsive drinking behaviour [29,32,33,118]. Supportive measures to avoid hyponatraemia are the following: ingestion of a balanced diet, avoidance of drugs that may cause a dry mouth, hence increasing drinking, and frequent weighing to detect water retention. Studies have investigated behavioural therapy such as disease education, relaxation training using biofeedback, conditioning of desired behaviour, group therapy and others [34–37] and have shown variable results. However, the feasibility of behavioural treatments, requiring substantial time and manpower, are limited in an outpatient setting [37].

Different medications have been suggested to improve polydiptic behaviour and prevent hyponatraemia. As PP has mainly been studied in acutely psychotic patients, it is not surprising that most drugs studied are antipsychotic drugs and mood stabilisers such as olanzapine, lithium, risperidone, aripiprazole and clozapine [36,38–43,119]. The question however remains whether these drugs are treating the urge to drink, or if they are simply reducing acute psychosis and thus treat PP that might be a symptom of acute psychosis. Other medications that have been found to reduce polydiptic behaviour are phenytoin, bupropion, and propranolol [44,45,120]. All therapeutic options studied are considered low evidence, as these are descriptions of case reports, small case series or small casecontrol group studies. In conclusion, the wide spread of different medication used underlines the difficulty in treating this disorder and the need for better options.

Acute treatment of hyponatraemia in PP primarily consists of fluid restriction. In cases of profound and symptomatic hyponatraemia, a 3% saline infusion may be used. Overcorrection of hyponatraemia (increase of serum sodium >12 mmol/24h) has been described in patients with PP, fortunately without neurological complications [111,121,122]. Nevertheless, treating physicians should be aware of the risk of overcorrection and consequently pontine myelinolysis.

Conclusion

In conclusion, the pathophysiology of PP is complex and poorly understood. PP is associated with a wide spectrum of psychiatric comorbidities beyond schizophrenia. Moreover, habitual polydipsia appears to be increasing in prevalence in lifestyle conscious healthy people. Several factors impairing water excretion exist and may promote hyponatraemia in PP, a condition linked to substantial morbidity and mortality.

Fluid restriction is a successful measure to correct the complication of acute hyponatraemia, however, in the long run treatment options for this typically chronic condition are scarce. Studies elaborating novel therapeutic approaches would be desirable. But most importantly, educational measures in the general population might be needed to rationalise the prevalent advice to “drink enough”.

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Manuscript I: Characteristics and outcomes of patients with profound hyponatraemia due to primary polydipsia

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Abstract

Objective Hyponatraemia due to excessive fluid intake (ie primary polydipsia [PP]) is common. It may culminate in profound hyponatraemia—carrying considerable risk of morbidity. However, data on patients with PP leading to hyponatraemia are lacking. Herein, we describe the characteristics of polydiptic patients hospitalized with profound hyponatraemia and assess 1-year outcomes.

Design Substudy of the prospective observational Co-MED Study.

Patients: Patients with an episode of profound hyponatraemia (≤125 mmol/L) due to PP in the medical emergency were eligible and classified into psychogenic polydipsia (PsyP), dipsogenic polydipsia (DiP) and beer potomania (BP).

Measurements Symptoms, laboratory findings and factors contributing to hyponatraemia (comorbidities, medication and liquid intake) were assessed. A 1-year follow-up was performed to evaluate recurrence of hyponatraemia, readmission rate and mortality.

Results Twenty-three patients were included (median age 56 years [IQR 50-65], 74% female), seven had PsyP, eight had DiP and eight had BP. Median serum sodium of all patients was 121 mmol/L (IQR 114-123), median urine osmolality 167 mmol/L (IQR 105-184) and median copeptin 3.6 mmol/L (IQR 1.9-5.5). Psychiatric diagnoses, particularly dependency disorder (43%) and depression (35%), were highly prevalent. Factors provoking hyponatraemia were found in all patients (eg acute water load, medication, stress).

During the follow-up period, 67% of patients were readmitted, 52% of these with rehyponatraemia, and three patients (38%) with BP died.

Conclusion Patients with PP are more likely to be female and to have addictive and affective disorders. Given the high recurrence, rehospitalization and mortality rate, careful monitoring and long-term follow-up including controls of serum sodium, education and behavioural therapy are needed.

Introduction

Primary polydipsia (PP) is defined as excessive ingestion of fluids (>3000 mL/d) and consecutive excretion of profound quantities of dilute urine [5]. PP was first described in patients with schizophrenia and has therefore been named “psychogenic polydipsia” (PsyP) [5]. Further categories have been reported as: individuals who voluntarily drink excessive fluids without psychiatric comorbidities (“dipsogenic polydipsia” [DiP]), individuals who increase drinking after receiving medical advice (“iatrogenic polydipsia”) and PP resulting from a brain injury or a pathological process in the hypothalamus or the pituitary gland (eg sarcoidosis or traumatic brain injury) [13,82,103,123]. A comparable pathology, seen in alcoholics and beer-binge drinkers, is characterized by the chronic or acute consumption of large amounts of beer and has been described as “beer potomania” (BP) [56]. As underlying pathophysiology, a dysfunction in the dopaminergic and cholinergic system has been discussed, resulting in a dysregulation of the thirst centre, as well as an involvement of the hippocampal region, leading to “bizarre behaviours” such as constant drinking [7,65,72,124].

Excessive fluid intake results in a decrease in serum osmolality and by inhibiting the release of the hormone arginine vasopressin (AVP) leads to hypotonic polyuria. The normal excretory capacity of the kidneys is about 12 L/d and can thus, in normal circumstances, compensate for the increased liquid intake [27]. However, this system might be influenced and changed by external factors. A potentially severe complication of excessive fluid intake is the onset of hyponatraemia [95]; 20%-30% of patients with schizophrenia and PP develop episodic or chronic hyponatraemia, which is mostly mild and oligosymptomatic [5,125]. Nevertheless, some patients may present with profound symptomatic hyponatraemia and neurological complications [31]. Several risk factors are thought to predispose hyponatraemia: chronicity of PP, acute ingestion of excessive quantities of water exceeding the maximum excretory function of the kidney per hour, nonosmotic AVP stimulation (eg psychosis, acute stress), smoking and drugs (eg antidepressants, antipsychotics, diuretics) [93,95,126]. A contributing factor is the low solute intake, which is typically observed in BP and malnourished people, leading to the reduction in the renal excretory capacity from 12 L/d to 8 L/d or less [27,62].

Little is known about chronic complications of continuous excessive fluid consumption, but bladder dilatation, hydronephrosis, renal failure, congestive heart failure, gastrointestinal dilatation and osteopenia with increased risk of fractures have been described [117].

Taken together, PP is thought to be associated with substantial morbidity, mortality and health service utilization [31,46]. However, consistent clinical data on patients with PP leading to hyponatraemia are lacking, information regarding presentation and outcomes being scarce. Most of the existing data arise from case reports and retrospective studies within a psychiatric setting.

The aim of this prospective study was therefore to describe clinical characteristics of patients with PP hospitalized in a general hospital with profound hyponatraemia and to assess outcomes 1-year post initial hospitalization.

Materials and methods

Study design

This is a predefined secondary analysis of a prospective multicentre observational study (Co-MED Study) including patients with profound hyponatraemia (≤125 mmol/L) in the medical emergency department of two tertiary care centres in Switzerland from June 2011 until August 2013 [127]. Of a total of 298 patients with profound hyponatraemia, we enclosed all patients in whom hyponatraemia was predominant due to PP (N=23).

Inclusion criteria were full legal age, profound hyponatraemia and diagnosis of PP, performed by experienced board-certified endocrinologists based on medical history (especially drinking habits), laboratory findings (serum <125 mmol/L and urinary osmolality <200 mmol/L), clinical examination and therapy response. Patients with secondary polydipsia (eg hyperglycaemia) were excluded. Patients were divided into the following groups: patients with primarily nonalcoholic fluid intake were diagnosed as PP and those consuming large amounts of beer as BP. Patients with PP were further classified as PsyP in the presence of psychiatric comorbidities and as DiP in the absence of psychiatric comorbidities.

Informed consent was obtained from all participants. The Ethics Committees of Basel and Aarau approved the study protocol. The study was preregistered on clinicaltrials.gov and was conducted per the current version of the Declaration of Helsinki, the ICH-GCP and all national legal regulatory requirements.

Clinical variables and follow-up: data collection

Medical history and symptoms related to hyponatraemia were recorded in specified bedside interviews. A clinical examination was performed, and data on vital parameters, electrolytes, current medication, comorbidities and social status were obtained immediately upon hospitalization. Therapy of PP, the course of serum sodium levels, ICU admission and mortality were assessed during the hospital stay. The ward physician not involved in the study was responsible for treatment of patients during hospitalization.

Follow-up was performed using a structured telephone interview and revising medical records 1 year after initial hospitalization to evaluate readmission rate, recurrence of hyponatraemia and mortality.

Study objectives

This study was intended to describe clinical and laboratory characteristics of patients hospitalized with profound hyponatraemia due to PP in a prospectively enrolled group. Special attention was paid to potential risk factors predisposing hyponatraemia, acute symptoms and complications related to

hyponatraemia, treatment and outcome 1 year after initial hospitalization. Defined outcome measures were readmission rate, recurrence of hyponatraemia and mortality.

Statistical analysis

All relevant clinical and laboratory parameters obtained by interview, clinical testing and review of medical records were entered for statistical analysis into an Excel database. Analyses were performed using R (Version 3.3.2 GUI 1.68 Mavericks build [7288], S. Urbanek & H.J. Bibiko, @ R Foundation for Statistical Computing, 2016).

Discrete variables are expressed as frequencies (percentage and number of participants, n), continuous variables as median and interquartile range (IQR 25th-75th percentiles), unless stated otherwise. Intergroup comparisons were performed using the Kruskal-Wallis or the Fisher's exact test, as appropriate. The significance level was set at $P<.05$.

Results

Baseline characteristics

Median age of all participants was 56 years (IQR 50-65), 74% were female. Sixty-five per cent were classified as primary polydipsia (PP) and 35% as beer potomania (BP), with 47% of PP patients being further classified as psychogenic polydipsia (PsyP) and the remaining 53% as dipsogenic polydipsia (DiP). All patients with PsyP and DiP were female (P<.001) and tended to be older (median age 60 years [IQR 52-69]) than patients with BP (median age 53 years [IQR 50-57], 25% female). The median reported fluid intake was 4350 mL/d (IQR 3000-5000) overall, 4000 mL/d (IQR 4000-5000) for patients with PsyP, 3000 mL/d (IQR 2000-3500) for patients with DiP and 5000 mL/d (IQR 4875-5250) for patients with BP.

Laboratory findings on hospital admission of all patients were as follows: median serum sodium of 121 mmol/L (IQR 114-123), median plasma osmolality of 256 mmol/L (IQR 248-261), median urinary osmolality of 167 mmol/L (IQR 105-184) and median urinary sodium of 21.5 mmol/L (IQR 14.3-37). The median copeptin level was 3.6 pmol/L (IQR 1.9-5.5). (Table 1).

TABLE 1 Baseline characteristics of 23 patients, classified as patients with psychogenic, dipsogenic polydipsia and beer potomania

Characteristics	All participants	Psychogenic polydipsia	Dipsogenic polydipsia	Beer potomania	*P*-value
n	23	7	8	8	
Age (yrs), median (IQR)	56 (50-65)	60 (52-63)	60 (53-73)	53 (50-57)	.55
Female, % (n)	74 (17)	100 (7)	100 (8)	25 (2)	**<.001**
Systolic blood pressure (mm Hg), median (IQR)	122 (110-144)	114 (107-126)	116 (103-144)	136 (122-147)	.26
Heart rate (beats per minute), median (IQR)	87 (76-96)	84 (68-94)	90 (83-94)	85 (76-99)	.73
Body temperature (°C), median (IQR)	37 (36.5-37.4)	37.2 (36.7-37.5)	37.1 (36.8-37.6)	36.9 (36.4-37.0)	.46
GCS, min-max	15 (13-15)	15 (15-15)	15 (15-15)	15 (13-15)	.06
BMI (kg/m^2), median (IQR)	22.6 (16.8-29.1)	16.2 (13.8-22.6)	23.5 (22.7-25.1)	29 (19.2-32)	.15
Reported amount of drinking/d (mL), median (IQR)	4350 (3000-5000)	4000 (4000-5000)	3000 (2000-3500)	5000 (4875-5250)	**.02**
Laboratory findings					
Serum sodium (mmol/L), median (IQR)	121 (114-123)	122 (120-123)	121 (119-123)	114 (111-123)	.61
Serum potassium (mmol/L), median (IQR)	3.9 (3.35-4.4)	3.9 (3.5-4.1)	3.7 (3.1-3.8)	4.6 (4.3-4.9)	**.01**
Plasma osmolality (mmol/L), median (IQR)	256 (248-261)	255 (249-258)	254 (247-261)	258 (240-276)	.47
Copeptin (pmol/L), median (IQR)	3.6 (1.9-5.5)	2.3 (1.8-3.1)	2.5 (1.4-5.1)	4.2 (3.7-7.3)	.19
Urinary sodium (mmol/L), median (IQR)	21.5 (14.3-37.3)	31.0 (18.8-41.8)	21.5 (13.0-29.8)	17.0 (13.8-35.8)	.47
Urine osmolality (mmol/L), median (IQR)	167 (105-184)	138 (94-180)	137 (93-187)	178 (130-184)	.53

CI, confidence interval; GCS, Glasgow Coma Scale; BMI, body mass index.
Data are presented as % (n) and median (IQR: 25th - 75th). Intergroup comparisons were made using the Kruskal-Wallis test for continuous and the Fisher's Exact test for binomial outcome. Bold *P* values represent statistically significant results.

Comorbidities and medication

Comorbidities of the study population are provided in Table 2. The most common comorbidities were psychiatric disorders (65%) such as substance dependency disorder (43%), depression (35%), schizophrenia (13%) and anorexia nervosa (13%). Substance use was ubiquitous within this population: together with alcohol dependency, all patients with BP were smokers, which is significantly higher compared to the other two groups with 29% smokers in the PsyP group and 38% in the DiP group

respectively (*P*-value .007). One person per group was known to have been using illicit drugs in the past. Further comorbidities included epilepsy (26%), renal (17%) and cardiac diseases (13%). Fifty-seven per cent with PsyP, 25% with DiP, and all patients with BP had experienced hyponatraemia in the past (*P*-value .013) (Table 2).

The following medications were recorded upon hospital admission known to predispose hyponatraemia: benzodiazepine (43%), antidepressant drugs (39%), diuretics (30%), antipsychotic drugs (26%), antiepileptic drugs (22%) and opioids (13%). Drug use was higher in the patient group with PsyP than with DiP or BP. Eighty-three per cent of all patients had at least one of these medications (Table 2).

TABLE 2 Comorbidities and medication of 23 patients, classified as patients with psychogenic polydipsia, dipsogenic polydipsia and beer potomania

	All participants	Psychogenic polydipsia	Dipsogenic polydipsia	Beer potomania	*P*-value
n	23	7	8	8	
Comorbidities					
Psychiatric disorder, % (n)	65 (15)	100 (7)	0 (0)	100 (8)	**<.001**
Dependency disorder, % (n)	48 (11)	43 (3)	0 (0)	100 (8)	**.01**
Depression, % (n)	39 (9)	86 (6)	0 (0)	38 (3)	.14
Personality disorder, % (n)	17 (4)	57 (4)	0 (0)	0 (0)	**.004**
Schizophrenia, % (n)	13 (3)	29 (2)	0 (0)	13 (1)	.27
Anorexia nervosa, % (n)	13 (3)	43 (3)	0 (0)	0 (0)	**.02**
Anxiety disorder, % (n)	9 (2)	0 (0)	0 (0)	25 (2)	.3
Bipolar disorder, % (n)	4 (1)	0 (0)	0 (0)	13 (1)	1
Epilepsy, % (n)	26 (6)	29 (2)	38 (3)	13 (1)	.62
Pulmonary disease, % (n)	17 (4)	14 (1)	13 (1)	25 (2)	1
Renal disease, % (n)	17 (4)	0 (0)	25 (2)	25 (2)	.49
Cardiac insufficiency, % (n)	13 (3)	14 (1)	0 (0)	25 (2)	.49
Hypertension, % (n)	48 (11)	29 (2)	38 (3)	75 (6)	.2
Hyponatraemia in the past, % (n)	61 (14)	57 (4)	25 (2)	100 (8)	**.013**
Smoking, % (n)	57 (13)	29 (2)	38 (3)	100 (8)	**.007**
Smoking amount (py), median (IQR)	40 (20-60)	20 (15-30)	20 (12-25)	59 (49-60)	**<.001**
Alcohol consumption, % (n)	57 (13)	29 (2)	38 (3)	100 (8)	**.007**
Medication					
Benzodiazepine, % (n)	43 (10)	57 (4)	25 (2)	50 (4)	.57
Benzodiazepine abuse, % (n)	17 (4)	29 (2)	0 (0)	25 (2)	.41
Antidepressant drugs, % (n)	39 (9)	86 (6)	0 (0)	38 (3)	**.002**
Antipsychotic drugs, % (n)	26 (6)	43 (3)	13 (1)	25 (2)	.43
Antiepileptic drug, % (n)	22 (5)	29 (2)	25 (2)	13 (1)	.84
Opioids, % (n)	13 (3)	29 (2)	0 (0)	13 (1)	.27
Diuretics, % (n)	26 (6)	29 (2)	25 (2)	38 (2)	1
No medication, % (n)	17 (4)	0 (0)	38 (3)	13 (1)	.27

IQR, interquartile range; py, pack years.

Data are presented as % (n) and median (IQR: 25th - 75th). Intergroup comparisons were made using the Kruskal-Wallis test for continuous and the Fisher's Exact test for binomial outcome. Bold *P* values represent statistically significant results.

Symptoms and therapy

The most common symptoms in our population were generalized weakness (65%), sensation of thirst (61%), nocturia (48%), nausea (39%) and gait disturbance (26%). Gait disturbance occurred significantly more often in patients with BP compared to the other groups (*P*=.012) (Table 3).

All participants received an initial treatment of free fluid restriction, combined with 0.9% saline in 57%. No patient received 3% saline. Median correction rate within the first 24 h was 6 mmol/L (IQR 4-10), two participants experienced overcorrection (increase of serum sodium level by 14 mmol/L and 20 mmol/L), nevertheless without clinical signs of pontine myelinolysis. Median serum sodium level at discharge was 135 mmol/L (IQR 132-138 mmol/L). Forty-eight per cent of all participants (41% of PP and 66% of BP) were discharged before a normal sodium level of >135 mmol/L was reached. Twenty-two per cent had to be admitted to the intensive care unit (ICU), 14% with PsyP, none with DiP and 50% with BP. Reasons for ICU admission were symptomatic hyponatraemia, a bone fracture due to an acute fall, alcohol abstinence delirium and respiratory problems. One patient of the group of BP died during the initial hospitalization due to sepsis caused by aspiration pneumonia (Table 3).

Two participants (29%) with PsyP had to be transferred to a psychiatric hospital for further treatment after correction of hyponatraemia.

TABLE 3 Symptoms at admission and therapy of 23 patients and subclassification as patients with psychogenic polydipsia, dipsogenic polydipsia and patients with beer potomania

	All participants	Psychogenic polydipsia	Dipsogenic polydipsia	Beer potomania	*P*-value
n	23	7	8	8	
Symptoms					
Generalized weakness, % (n)	65 (15)	71 (5)	50 (4)	75 (6)	.66
Sensation of thirst, % (n)	61 (14)	71 (5)	63 (5)	50 (4)	.87
Nocturia, % (n)	43 (10)	57 (4)	38 (3)	38 (3)	.76
Concentration disorder, % (n)	39 (9)	29 (2)	38 (3)	50 (4)	.87
Headache, % (n)	30 (7)	14 (1)	50 (4)	25 (2)	.4
Nausea, % (n)	39 (9)	43 (3)	38 (3)	38 (3)	1
Vomitus, % (n)	26 (6)	29 (2)	38 (3)	13 (1)	.62
Diarrhoea, % (n)	39 (9)	29 (2)	50 (4)	38 (3)	.87
Gait disturbance, % (n)	26 (6)	14 (1)	0 (0)	63 (5)	**.012**
Recurrent falls, % (n)	17 (4)	14 (1)	0 (0)	38 (3)	.17
Acute fall, % (n)	9 (2)	14 (1)	0 (0)	13 (1)	.75
Bone fracture, % (n)	4 (1)	14 (1)	0 (0)	0 (0)	.3
Muscle cramp, % (n)	17 (4)	14 (1)	13 (1)	25 (2)	1
Seizure, % (n)	4 (1)	0 (0)	13 (1)	0 (0)	1
Therapy					1
Free fluid restriction, % (n)	100 (23)	100 (7)	100 (8)	100 (8)	.1
Amount of drinking d 1 (mL/d), median (IQR)	1500 (1000-1800)	1000 (820-1375)	1500 (850-1500)	1800 (1500-2500)	.49
Substitution of isotonic solution (0.9%), % (n)	57 (13)	43 (3)	50 (4)	75 (6)	**.049**
ICU admission, % (n)	22 (5)	14 (1)	0 (0)	50 (4)	.09
Time until Na>130 mmol/L (d), median (IQR)	3 (2-4)	2.5 (1.3-8.25)	2 (1-3)	4 (2.8-6.3)	.27
Natrium at discharge (mmol/L)	135 (133-139)	137 (133-140)	135 (134-139)	133 (130-138)	.66
Natrium >135 mmol/L at discharge, % (n)	74 (17)	86 (6)	75 (6)	63 (5)	.87

ICU, intensive care unit; IQR, interquartile range.
Data are presented as % (n) and median (IQR: 25th - 75th). Intergroup comparisons were made using the Kruskal-Wallis test for continuous and the Fisher's Exact test for binomial outcome. Bold *P* values represent statistically significant results.

Factors contributing to the development of hyponatraemia

Possible factors contributing to the development of hyponatraemia were found in every patient. Besides an impaired water excretory capacity due to malnutrition, the main reason was a concomitant stimulus for AVP. All patients with PsyP, 75% with DiP and 63% with BP were found to have medications potentially stimulating AVP. Another common nonosmotic AVP stimulus was an acute infection (pneumonia or urogenital tract infection) in 50% of patients with DiP and 38% with BP. Further trigger factors for AVP were nausea (39%), reduced GCS, a transitory ischaemic attack (TIA) and a seizure. None of the patients suffered from an acute psychotic episode (Table 4).

TABLE 4 Possible factors contributing to the development of hyponatraemia of 23 patients, classified as patients with psychogenic, dipsogenic polydipsia and beer potomania

Factor causing hyponatraemia	All participants	Psychogenic polydipsia	Dipsogenic polydipsia	Beer potomania	*P*-value
n	23	7	8	8	
Acute fluid intake, % (n)	13 (3)	14 (1)	0 (0)	25 (2)	.494
Impaired water excretion, % (n)	100 (23)	100 (7)	100 (8)	100 (8)	1
Low solute intake, n (%)	52 (12)	57 (4)	0 (0)	100 (8)	**<.001**
Concomitant AVP stimulus, n (%)	100 (23)	100 (7)	100 (8)	100 (8)	1
Medication, n (%)	78 (18)	100 (7)	75 (6)	63 (5)	.3
Pneumonia/COPD exacerbation, n (%)	17 (4)	0 (0)	13 (1)	38 (3)	.27
UGT infection, n (%)	17 (4)	14 (1)	38 (3)	0 (0)	.17
Nausea/Vomitus, n (%)	39 (9)	43 (3)	38 (3)	38 (3)	1
Acute psychosis, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1

AVP, vasopressin; COPD, chronic obstructive pulmonary disease; UGT, urogenital tract.
Data are presented as % (n) and median (IQR: 25th - 75th). Intergroup comparisons were made using the Kruskal-Wallis test for continuous and the Fisher's Exact test for binomial outcome. Bold *P* values represent statistically significant results.

One-year follow-up of primary polydipsia

Complete follow-up data were available for 21 participants (91%). Sixty-six per cent of the patients with PsyP were readmitted to the hospital, 25% at least twice and 50% experienced another episode of hyponatraemia. In the patient's group with DiP, 43% were rehospitalized: 33% more than once and 66% with another episode of hyponatraemia. All patients with BP were readmitted to the hospital, 57% more than once and all had another episode of hyponatraemia. Mortality rate in BP was 38%: one patient died during the initial hospitalization, two more throughout the follow-up year, one due to complications of an abdominal surgery and the other for unknown reasons. None of the patients seemed to have died directly due to hyponatraemia (Table 5).

TABLE 5 One-year follow-up of 23 patients and subclassifications as psychogenic polydipsia, dipsogenic polydipsia and beer potomania

Follow-up	All participants	Psychogenic polydipsia	Dipsogenic polydipsia	Beer potomania	*P*-value
n	21	6	7	8	
Rehospitalization, % (n)	67 (14)	66 (4)	43 (3)	88 (7)	.21
Recurrent rehospitalization, % (n)	43 (6)	25 (1)	33 (1)	57 (4)	.28
Rehyponatraemia, % (n)	79 (11)	50 (2)	66 (2)	100 (7)	.47
Profound hyponatraemia (<125 mmol/L), % (n)	36 (5)	25 (1)	0 (0)	57 (4)	.08
Time until first rehospitalization, % (n)	66 (29-125)	108 (27-142)	110 (80-138)	57 (25-95)	.55
Mortality rate, % (n)	14 (3)	0 (0)	0 (0)	38 (3)	.08

Data are presented as % (n) and median (IQR: 25th - 75th). Intergroup comparisons were made using the Kruskal-Wallis test for continuous and the Fisher's Exact test for binomial outcome. Bold *P* values represent statistically significant results.

Discussion

To our knowledge, this is the first prospective study on patients with increased fluid consumption leading to hyponatraemia in a medical emergency setting. We herein present the following main findings: first, patients with excessive fluid intake exhibit a wide spectrum of mostly psychiatric comorbidities. Second, in hyponatraemic patients with polydipsia several risk factors impairing water excretion and promoting hyponatraemia, respectively, are present. Third, compulsive fluid ingestion is a chronic disorder and associated with substantial morbidity and mortality.

In our population, psychiatric diagnoses were prevalent in patients with PsyP and BP. Of note, all patients with PsyP and DiP were female, while patients with BP were mostly male. Psychiatric patients especially with chronic schizophrenia are known to be at risk of suffering from PsyP [30,31,128]. Here, only few patients had such a diagnosis. In contrast, the most prevalent psychiatric disorder was dependency disorder. Given that compulsive fluid ingestion per se could be seen as an addictive behaviour, this seems likely and is supported by a high prevalence of smoking in this and other studies [31].

Another frequent psychiatric disorder was depression. Only one case report describes PsyP in the context of depression [129]. The association of depression and PsyP could be explained by a hippocampal involvement, a brain region involved in affective disorders, which modulates the AVP response to stress[25,65,130]. An alternative explanation could be the anticholinergic side effects of antidepressants causing an elevated sensation of thirst.

Interestingly, three patients with PsyP had a diagnosis of anorexia nervosa. Further, two patients had a BMI <17.5 kg/m2. Patients with anorexia nervosa may increase liquid consumption to compensate for low food intake and to decrease the sensation of hunger. Similarities of anorexia nervosa and BP—characterized by malnutrition with low protein and high liquid intake—are striking. A minimum of solutes (50-60 mmol/L) is necessary for a normal renal function with adequate water clearance. Hence, in people with anorexia, BP or malnutrition, the low solute intake increases the risk of hyponatraemia [27], especially when combined with high fluid ingestion.

Surprisingly, one-third of the patients had no psychiatric comorbidity and were categorized into the DiP group. This is an interesting finding, because until now, polydipsia has mainly been studied in the psychiatric setting. Although most DiP patients might not experience hyponatraemia, special situations associated with (AVP-stimulating) stress, such as acute illness, may put them at risk to develop hyponatraemia. Interestingly, there is an increasing number of case reports describing patients with DiP who develop hyponatraemia during an acute infection (eg pneumonia, urogenital tract infection) [101,102]. Educative measures in the general population might be needed to rationalize the prevalent advice to “drink a lot in acute illnesses” and the required amount of drinking, especially in acute illnesses, should be further investigated.

In all groups, patients with the diagnosis of epilepsy were present. One of these patients experienced an acute seizure presumably due to hyponatraemia [131]. Beyond this acute complication, a probable association of temporal epilepsy and peri-ictal water consumption has been suggested [132]. The development of hyponatraemia in these patients might also be due to antiepileptic drugs.

Even in the presence of profound hyponatraemia, patients declared a sensation of thirst. This emphasizes that PP is caused by a dysfunction in the thirst centre [124], and that the osmotic threshold of thirst perception is depressed below the osmotic threshold for AVP secretion [133]. Alternatively, it might mirror a behavioural misperception associated with the chronic urge to drink. Suppression of AVP and thus maximally suppressed urine osmolality are expected during increased consumption of liquid. In our study, urine osmolality remained unexpectedly high. It has been shown that patients with PP who become hyponatraemic have a higher urine osmolality than patients with PP who remain normonatraemic, indicating insufficient AVP suppression [28,30]. Underlining the nonosmotic AVP stimulus in our patients, we found nonsuppressed copeptin levels. Copeptin, a stable and reliable surrogate marker of AVP [134], has been shown to be high in other aetiologies of hyponatraemia in the Co-MED study: the median copeptin values were 36.7 pmol/L (IQR 12.09-88.30 pmol/L) in hypovolaemic hyponatraemia, 28.15 pmol/L (IQR 12.42-64.45 pmol/L) in hypervolaemic hyponatraemia and 11.87 pmol/L (IQR 5.35-27.20 pmol/L) in SIADH (syndrome of inappropriate antidiuretic hormone secretion) [127]. We hypothesize that for patients with PP to become hyponatraemic, a certain AVP stimulus is needed. Such a stimulus could be physical (eg acute infection) or psychological stress (eg acute psychosis), drugs (eg antidepressants, antipsychotics) or smoking. Every patient had at least one of these stimuli.

Copeptin levels were slightly higher in BP compared to the other two groups. As copeptin is also a stress hormone, the more severe illness in BP patients (more comorbidity and reduced GCS) could be one explanation. Alternatively, the predominance of male gender could explain the higher copeptin levels, as men generally show higher copeptin values than women.

Therapy with fluid restriction was successful in all patients to raise sodium levels; none needed treatment with hypertonic saline. Some patients were admitted to the ICU for close monitoring of sodium levels, while other patients were admitted to the ICU not due to their hyponatraemia symptoms but because of comorbidities.

Our third main finding is an unfavourable 1-year outcome, particularly in patients with BP. Within 1 year, most patients had to be rehospitalized at least once, and recurrent hyponatraemia was common. In patients with BP the mortality rate was high, although cause of death seemed not directly related to hyponatraemia itself. The electrolyte disturbance may also be interpreted as marker of disease severity in this context [58].

The high recurrence of hyponatraemia and rehospitalization rate highlights the chronicity of PP and illustrates that simply correcting hyponatraemia is insufficient in these patients. Patients with PP may benefit from a longer follow-up with focus on cognitive behavioural therapy to treat excessive fluid intake and identification of hyponatraemia predisposing factors (eg concomitant drugs, comorbidities, behavioural misconceptions in the general population) to prevent development of hyponatraemia.

Strengths and limitations

Several limitations should be considered for the interpretation of our results. First, the design of a secondary analysis of an observational study increases the risk of biases. Second, the limited number of people with PP should be considered when extrapolating the results to the population. Third, to discriminate PP from SIADH, a cut-off limit for urinary osmolality of 100 mmol/l is proposed in the current guidelines for hyponatraemia [135,136]. We and others [123] use a higher cut-off of 200 mmol/L which might have led to misclassification. Nevertheless, final diagnosis of PP was not only based on urinary osmolality, but included all available clinical and laboratory information. We believe that the predominant cause in our patients was polydipsia, but an additional component of a SIADH might have been present. Fourth, the half-life of copeptin is not known but supposed to be longer than the half-life of AVP; thus, we cannot exclude that the nonsuppressed copeptin levels in the presence of acute water load seen in our patients are explained by its longer half-life. Fifth, most of the patients did not have a cerebral imaging, and thus we might have underestimated patients with hypothalamic/pituitary lesions. Fifth, we probably underestimated the proportion of psychotic patients, as they might have been treated in a psychiatric hospital. Strengths of our study include the prospective design, which allowed us to carefully diagnose and characterize patients with PsyP, DiP and BP, and the investigation of polydiptic patients outside a psychiatric setting.

Conclusion

Excessive fluid intake is a complex medical condition, which may lead to life-threatening hyponatraemia especially when exposed to AVP stimulus and/or reduced renal excretory capacity. Primary polydipsia is not only present in patients with schizophrenia spectrum disorder but also in a wider range of psychiatric diagnosis. Specifically, we found a high prevalence of addictive and affective disorders in our patients—the interplay between these disorders with PP and hyponatraemia should be elucidated in further studies. Nevertheless, one-third did not suffer from a psychiatric disorder. Given the high recurrence, rehospitalization and mortality rate especially in patients with BP, longer follow-up, including controls of serum sodium, education (regarding eating and drinking habits) and behavioural therapy must be integrated in current therapeutic approaches.

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Conflict of interest

Thermo Scientific Biomarkers, Hennigsdorf, Germany (formerly B.R.A.H.M.S AG), the copeptin assay developer/manufacturer, performed copeptin testing using reagents that it supplied at no charge. Dr Schuetz, Dr Mueller and Dr Christ-Crain have received speaker honoraria and research support from Thermo Scientific Biomarkers. The other authors reported no conflict of interests.

Manuscript II: Influence of Outdoor Temperature and Relative Humidity on Incidence and Etiology of Hyponatremia

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Abstract

Context Hyponatremia is the most common electrolyte disturbance in hospitalized patients. Known risk factors are heart or renal failure, excessive drinking, or the use of diuretics. The incidence of hyponatremia may also be influenced by climate.

Objective Analyzing the influence of outdoor temperature and relative humidity on the incidence and etiology of hyponatremia.

Design: Cohort A: cross-sectional study from January 2011 to December 2016. Cohort B: prospective observational study from June 2011 to August 2013.

Setting Emergency departments of two tertiary centers.

Patients Cohort A: patients with plasma sodium ≤145 mmol/L (n = 222,217). Cohort B: consecutive patients (n = 294) with profound hyponatremia (plasma sodium ≤125 mmol/L).

Main Outcome Measure The effects of outdoor temperature and relative humidity on the incidence of mild (sodium 126 to 134 mmol/L) and profound hyponatremia (sodium ≤125 mmol/L) were investigated via logistic regression models. The effects of outdoor temperature and relative humidity on hyponatremia etiology were evaluated.

Results In cohort A, 9.9% had mild and 1.08% had profound hyponatremia. Outdoor temperature was significantly associated with the incidence of profound but not mild hyponatremia ($P < 0.01$, $P = 0.3$). Relative humidity was not associated with the incidence of hyponatremia. In cohort B, diuretic-induced hyponatremia occurred more frequently with higher outdoor temperatures, whereas other etiologies showed no clear variation with outdoor temperature or relative humidity.

Conclusions Higher outdoor temperature, but not relative humidity, seems to be associated with the incidence of profound hyponatremia. Our data suggest that diuretics should be used with caution during hot weather.

Introduction

Hyponatremia is the most common electrolyte disorder and is associated with increased morbidity and mortality [58,135,137]. The incidence of mild hyponatremia (plasma sodium 126 to 134 mmol/L) ranges from 10% to 30%, and the incidence of profound hyponatremia (plasma sodium ≤125 mmol/L) ranges from 1% to 5% [137–141]. Risk factors for hyponatremia, such as heart or liver failure, excessive drinking, dehydration, drugs, intense physical activity, and age, have been identified [135,141–143]. It has also been speculated that the incidence of hyponatremia varies with climate factors (eg, outdoor temperature, relative humidity) [144–147]. In line with this speculation, the highest incidence of hyponatremia has been reported in tropical Asia and Australia [140,141]. In Europe, two retrospective observational studies found a higher incidence of profound hyponatremia cases in the summer compared with the winter [144,146]. Another study showed a higher incidence of hyponatremia in older adults in the summer [145], and two other studies found higher rates of hyponatremia during heatwaves [148,149].

However, these studies focused mostly on a small or specific group (eg, profound hyponatremia, older adults), and the etiology of hyponatremia [*ie*, syndrome of inappropriate antidiuresis (SIAD), diuretic-induced hyponatremia, primary polydipsia-induced hyponatremia] in association with outdoor temperature or relative humidity has not yet been studied prospectively. Climate change has increased outdoor temperature and the frequency of weather extremes [150]. A possible association between climate and the incidence of hyponatremia might therefore become even more important in the future.

Therefore, the current study aimed at investigating the potential influence of outdoor temperature and relative humidity on the incidence of mild and profound hyponatremia in a broad general medical collective and the impact of outdoor temperature and relative humidity on the etiology of hyponatremia.

Materials and methods

Study design

We analyzed data from two patient cohorts.

Cohort A

A cross-sectional study included patients with a plasma sodium measured in the emergency departments of two tertiary care centers in Switzerland between January 2011 and December 2016. We defined normonatremia as plasma sodium levels between 135 and 145 mmol/L, mild hyponatremia as plasma sodium levels between 126 and 134 mmol/L, and profound hyponatremia as plasma sodium levels ≤125 mmol/L. We excluded patients with hypernatremia (plasma sodium >145 mmol/L).

Cohort B

A prospective observational study included consecutive patients with profound hyponatremia (plasma sodium ≤125 mmol/L) admitted to the medical emergency department of the same two centers in Switzerland from June 2011 to August 2013.

The Ethics Committees of Basel and Aarau approved the study protocol (NCT01456533). The study was registered on clinicaltrials.gov. All participants in cohort B gave written informed consent before study inclusion, as recommended by the Declaration of Helsinki. The study was conducted according to the International Conference on Harmonisation–Good Clinical Practice and all national legal regulatory requirements.

Data collection

Cohort A

The following data were obtained from an electronic registry: date of admission to the emergency department, age, sex, and initial plasma sodium level.

Cohort B

Collected data included medical history, symptoms related to profound hyponatremia, vital parameters, volume status, blood sampling, medication, and comorbidities. Based on the collected clinical data, the etiology of profound hyponatremia was determined by experienced, board-certified endocrinologists in a structured and standardized fashion. Hyponatremia was classified as SIAD, diuretic-induced hyponatremia, hypovolemic hyponatremia (dehydration), hypervolemic hyponatremia (heart and liver failure), and primary polydipsia-induced hyponatremia.

Meteorological data

We received mean daily outdoor temperature and mean daily relative humidity from the official weather services of Switzerland and the open data repository of the Federal Office of Meteorology and Climatology MeteoSwiss (Bundesamt für Meteorologie und Klimatologie MeteoSchweiz). The measurements were recorded within 3.4 km and 2.5 km of the participating hospitals, respectively.

Study objective and outcome measures

The main objective was to investigate the association of outdoor temperature and relative humidity with the incidence of mild and profound hyponatremia and with the etiology of hyponatremia. Outcome measures were mean daily outdoor temperature and mean daily relative humidity and, in view of seasonal variation, mean monthly outdoor temperature and mean monthly relative humidity.

Statistical analysis

Discrete variables are expressed as frequencies (percentage and number of participants, n), continuous variables as median and interquartile range (IQR, 25th to 75th percentiles). Univariate logistic regression models were used to assess the association between mean daily outdoor temperature and mean daily relative humidity on the incidence of mild and profound hyponatremia and on the etiology of profound hyponatremia. A multiple logistic regression model was used for mild and profound hyponatremia adjusted for age and sex. The continuous variables outdoor temperature, relative humidity, and age were centered on the respective mean. To assess the seasonal variation, we computed the incidence of hyponatremia per month and the mean monthly outdoor temperature and mean monthly relative humidity (mean of mean daily outdoor temperature and relative humidity).

Graphical analysis was done via locally estimated scatterplot smoothing (LOESS) to correlate outdoor temperature with the incidence of mild and profound hyponatremia.

Statistical significance was considered for a two-sided P value <0.05. Analyses were performed in R statistical software (MathSoft, Seattle, WA).

Results

Baseline characteristics

Cohort A

A total of 222,217 patients [median age 58 years (IQR 40 to 75), 47.8% female] with a measurement of plasma sodium ≤145 mmol/L were included in the analysis (Table 1). The incidence of mild hyponatremia was 9.9%, patients had a median plasma sodium of 132 mmol/L (IQR 130 to 134) and a median age of 71 years (IQR 57 to 81), and 51.2% were women. The incidence of profound hyponatremia was 1.08%, patients had a median plasma sodium of 122 mmol/L (IQR 119 to 124) and a median age of 72 years (IQR 60 to 81), and 58.4% were women. Mean daily outdoor temperature was 12.5°C for patients with mild hyponatremia and 14.2°C for patients with profound hyponatremia. Mean daily relative humidity was 79% for patients with mild hyponatremia and 77% for patients with profound hyponatremia (Table 1).

Table 1. Cohort A Baseline Characteristics

Cohort A	Total	Normonatremia	Mild Hyponatremia	Profound Hyponatremia	*P*
N (%)	222,217 (100)	197,890 (89)	21,928 (9.9)	2399 (1.08)	
Age, median (IQR)	58 (40–75)	56 (38–74)	71 (57–81)	72 (60–81)	**<0.001**
Female sex, n (%)	106,214 (47.8)	93,591 (47.3)	11,222 (51.2)	1401 (58.4)	**<0.001**
Median plasma sodium, mmol/L, median (IQR)	139 (137–141)	140 (138–141)	132 (130–134)	122 (119–124)	**<0.001**
Mean daily outdoor temperature, °C, median (IQR)	12.8 (5.9–18.7)	12.8 (5.9–18.6)	12.5 (5.9–18.8)	14.2 (6.2–19.6)	**<0.001**
Mean daily relative humidity, %, median (IQR)	78 (68–85)	78 (68–85)	79 (69–87)	77 (67–85)	**<0.001**

Three-group comparison between normonatremia, mild hyponatremia, and profound hyponatremia was done with the Kruskal-Wallis test. A two-sided $P < 0.05$ was considered statistically significant and appears in boldface.

Cohort B

A total of 294 participants were included in this analysis [127]. Patients had a median plasma sodium of 120 mmol/L (IQR 116 to 123) and a median age of 71 years (IQR 60 to 80), and 65.6% were women (Table 2). The most common etiology of hyponatremia was SIAD with 35.7% (n = 105), followed by diuretic-induced hyponatremia with 24.1% (n = 71), hypovolemic hyponatremia with 21.1% (n = 62), hypervolemic hyponatremia with 10.9% (n = 32), and primary polydipsia-induced hyponatremia with 8.2% (n = 24).

Table 2. Cohort B Baseline Characteristics

Cohort B	Total
n	294
Age, y, median (IQR)	71 (60–80)
Female sex, n (%)	193 (65.6)
Median plasma sodium, mmol/L, median (IQR)	120 (116–123)
Mean daily outdoor temperature, °C, median (IQR)	13.9 (5.6–20.8)
Mean daily relative humidity, %, median (IQR)	76 (68–85)
Etiology of profound hyponatremia	
SIAD, n (%, 95% CI)	105 (35.7, 30.1–41.5)
Diuretic-induced hyponatremia, n (%, 95% CI)	71 (24.1, 19.5–29.5)
Hypovolemic hyponatremia, n (%, 95% CI)	61 (21.1, 16.7–26.3)
Hypervolemic hyponatremia, n (%, 95% CI)	32 (10.9, 7.7–15.2)
Primary polydipsia-induced hyponatremia, n (%, 95% CI)	24 (8.2, 5.4–12.1)

Association of hyponatremia with outdoor temperature and relative humidity

Cohort A

The incidence of mild hyponatremia did not significantly correlate with outdoor temperature (OR 1, P = 0.9) or with relative humidity (OR 0.99, P = 0.07), in a univariate or a multiple logistic regression model adjusted for age and sex (Table 3, Figs. 1A, 2A).

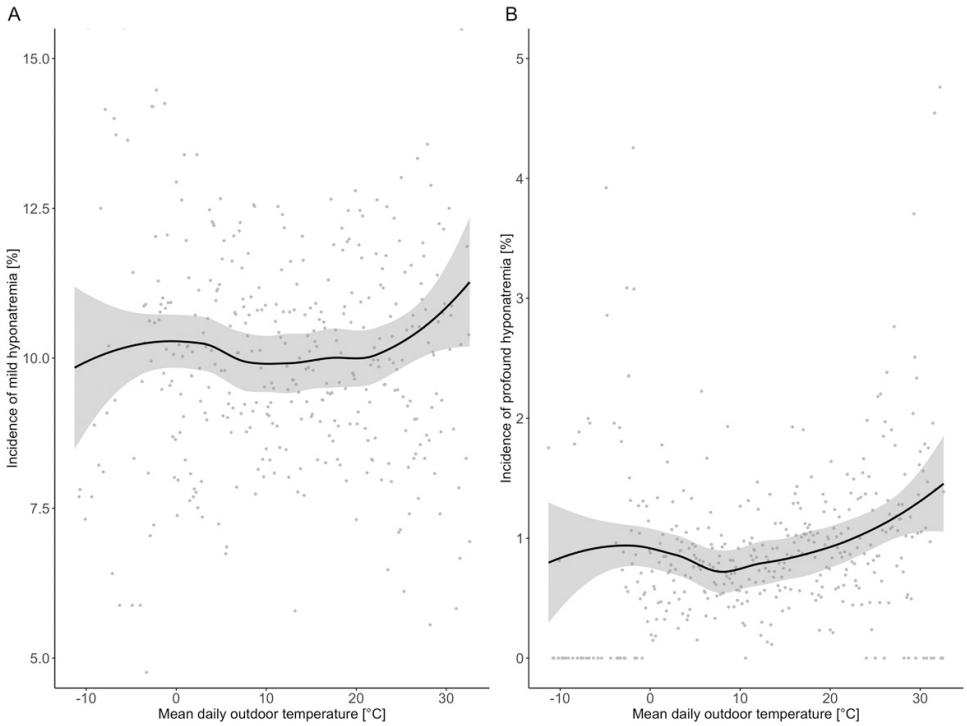

Figure 1. Incidence of mild and profound hyponatremia with outdoor temperature. Incidence (%) of (A) mild hyponatremia (plasma sodium 126 to 134 mmol/L) and (B) profound hyponatremia (plasma sodium ≤125 mmol/L) over mean daily outdoor temperature according to the LOESS method of smoothing.

Table 3. Univariate and Multiple Logistic Regression Analysis for Incidence of Mild Hyponatremia

	Univariate Logistic Regression Analysis		Multiple Logistic Regression Analysis	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Outdoor temperature	1 (0.998–1.002)	0.9	1.001 (1–1.003)	0.31
Relative humidity	0.99 (0.998–1.00)	0.07	0.999 (0.997–1.0)	0.07
Age	1.029 (1.028–1.029)	**<0.001**	1.029 (1.028–1.029)	**<0.001**
Female sex	1.16 (1.13–1.19)	**<0.001**	1.08 (1.054–1.12)	**<0.001**

A two-sided *P* <0.05 was considered statistically significant and appears in boldface.

Considering the incidence of profound hyponatremia, the univariate logistic regression model indicated a statistically significant positive correlation of outdoor temperature with a 1.2% increased risk per degree Celsius (OR 1.012, P , 0.001) and a statistically significant negative correlation of relative humidity with a 1% decreased risk per percentage point of relative humidity (OR 0.99, P , 0.001; Fig. 2B, Fig. 2B). Temperature remained statistically significant in the multiple regression model adjusted for age and sex, whereas relative humidity did not (Table 4).

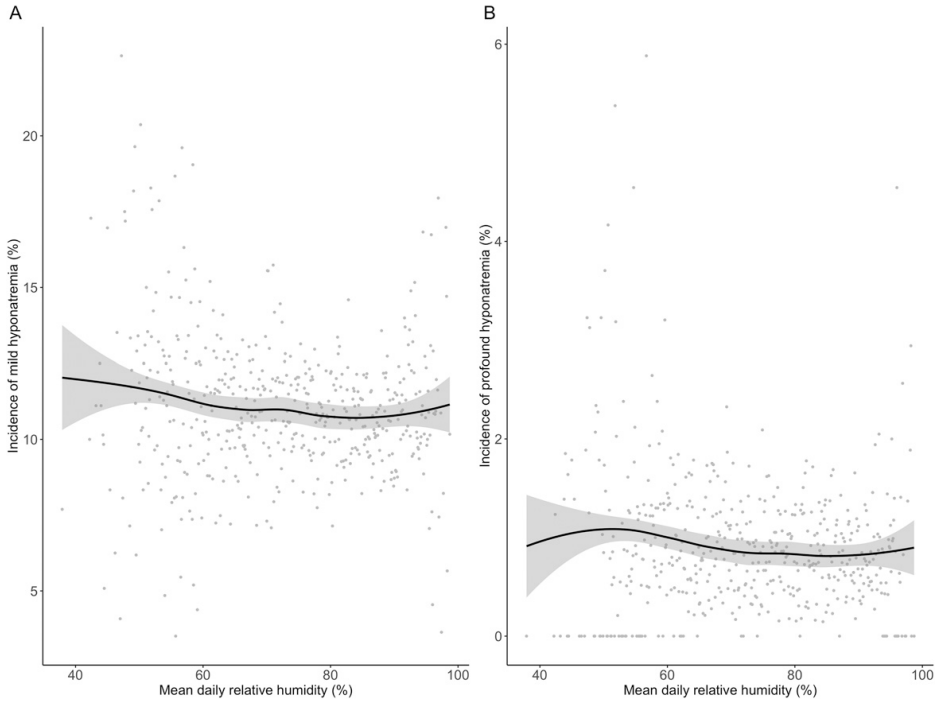

Figure 2. Incidence of mild and profound hyponatremia with relative humidity. Incidence (%) of (A) mild hyponatremia (plasma sodium 126 to 134 mmol/L) and (B) profound hyponatremia (plasma sodium ≤125 mmol/L) over mean daily relative humidity according to the LOESS method of smoothing.

Table 4. Univariate and Multiple Logistic Regression Analysis for Incidence of Profound Hyponatremia

	Univariate Logistic Regression Analysis		Multiple Logistic Regression Analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Outdoor temperature	1.012 (1.007–1.017)	**<0.001**	1.012 (1.006–1.017)	**<0.001**
Relative humidity	0.99 (0.99—0.997)	**<0.001**	0.997 (0.99–1.00)	0.1
Age	1.033 (1.031—1.036)	**<0.001**	1.032 (1.030–1.035)	**<0.001**
Female sex	1.54 (1.42—1.67)	**<0.001**	1.41 (1.3–1.5)	**<0.001**

A two-sided *P* <0.05 was considered statistically significant and appears in boldface.

Mean monthly outdoor temperature in the winter was about 3°C and increased in summer to 22°C. Conversely, mean relative humidity in the winter was about 85% and decreased in summer to 69%. Investigating the monthly incidence of hyponatremia, we observed no clear change of mild hyponatremia but a clear increase of profound hyponatremia during the summer (June, July, August) and a slight increase in profound hyponatremia in November (Fig. 3).

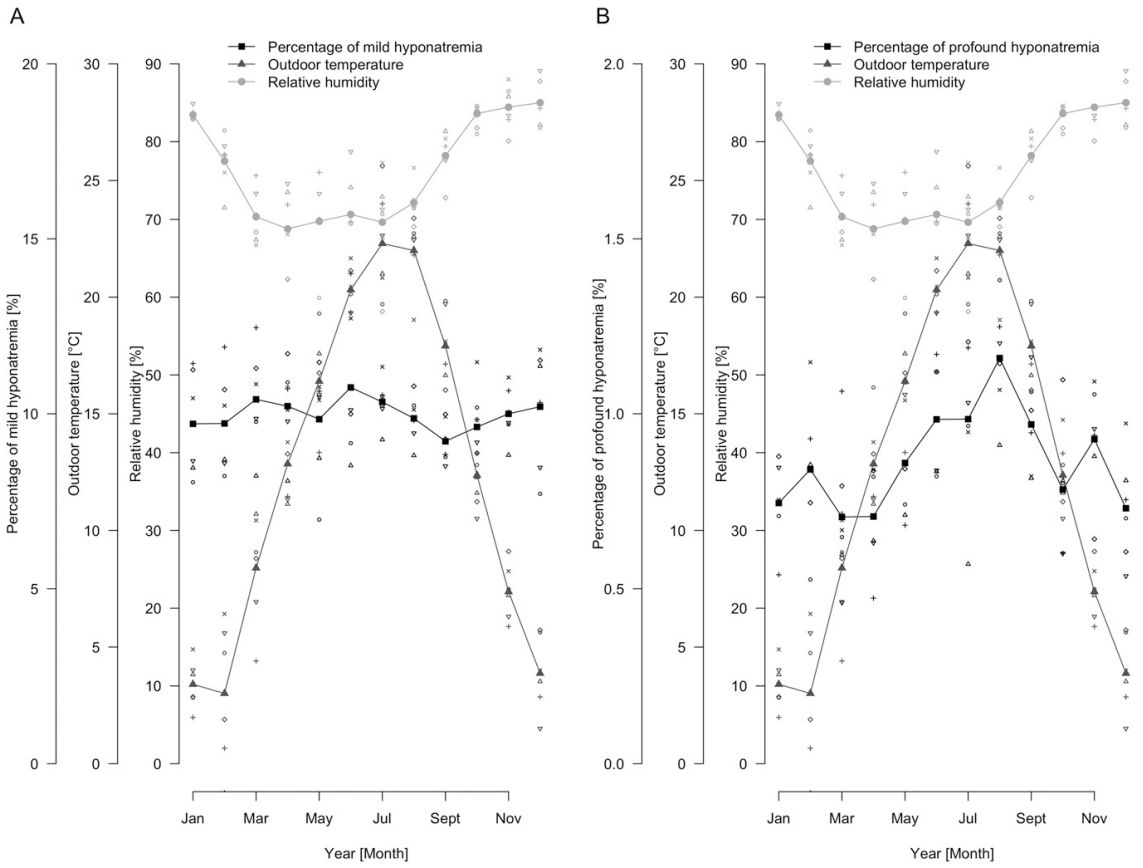

Figure 3. Seasonal variation of mild and profound hyponatremia. Monthly incidence of (A) mild hyponatremia and (B) profound hyponatremia over the study period of 7 y. The black curve and squares show the incidence of hyponatremia (%), the dark gray curve and triangles show the mean monthly outdoor temperature (°C), and the gray curve and round dots show the mean monthly relative humidity (%).

Association of the etiology of hyponatremia with outdoor temperature and relative humidity

Cohort B

The etiology of profound hyponatremia according to outdoor temperature is displayed in Fig. 4. The occurrence of diuretic-induced hyponatremia (n = 71) increased significantly, by 4% per degree Celsius of outdoor temperature (OR 1.04, P = 0.02). Primary polydipsia-induced hyponatremia seemed to be more common when outdoor temperatures ranged from 17°C to 22°C, but the association did not reach statistical significance. The other etiologies showed no clear difference with change in outdoor temperature. Considering relative humidity, no clear difference in etiology distribution of profound hyponatremia was found (data not shown).

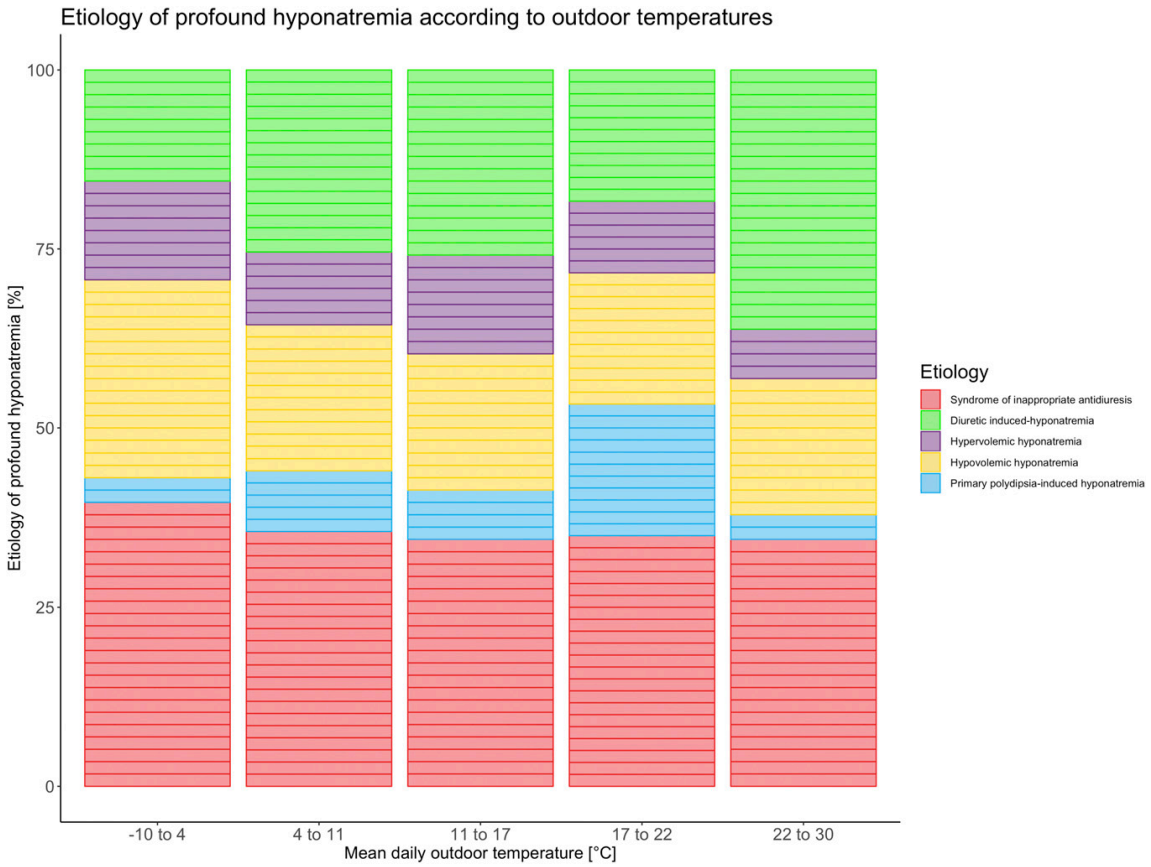

Figure 4. Etiology of profound hyponatremia according to outdoor temperature. The etiologies of hyponatremia in 5 categories of outdoor temperature. The red part represents patients with SIAD, the blue part represents patients with primary polydipsia-induced hyponatremia, the yellow part represents patients with hypovolemic hyponatremia, the violet part represents hypervolemic hyponatremia, and the green part represents diuretic-induced hyponatremia.

Discussion

The study has several findings. First, we found a positive correlation between outdoor temperature and the incidence of profound hyponatremia, with a seasonal increase in summer. Second, mild hyponatremia did not correlate with outdoor temperature, and no seasonal variation was detected. Third, hyponatremia due to diuretics was more frequently observed with higher outdoor temperatures. Fourth, humidity did not consistently correlate with the incidence of hyponatremia.

In line with previous studies, we hereby confirm in a large multicenter study that the incidence of profound hyponatremia increases with rising outdoor temperature [144,145]. One study from Switzerland showed a higher incidence of profound hyponatremia during hot weather [144], and one study from India indicated a higher incidence of profound hyponatremia during the warmer season [146]. Interestingly, mild hyponatremia seems less associated with outdoor temperature. The association of outdoor temperature and mild hyponatremia has been investigated in only one study from southern Europe, showing an increased prevalence of mild hyponatremia in older adults in summer [145]. To explain this difference, one might argue that patients with profound hyponatremia are generally sicker and more vulnerable to external stressors such as

extreme outdoor temperatures. Indeed, according to the j-shaped curve in Fig. 2B and the slight increase in hyponatremia incidence in November, our data suggest that profound hyponatremia increases with not only high temperatures but to a certain extent also with low temperatures. Another explanation might be that the etiologies of mild and profound hyponatremia differ [58] and that the various underlying diseases are differently susceptible to outdoor temperature. According to a previous publication, milder hyponatremia is often caused by heart or liver failure, whereas more profound hyponatremia seems mostly drug-induced [58].

In line with the latter finding, our results suggest that diuretic-induced profound hyponatremia occurs more frequently with increased outdoor temperature. In contrast, we did not find a temperature dependence of hypervolemic or hypovolemic hyponatremia or of SIAD. Similarly, Huwyler et al. [144] and Jönsson et al. [147] showed an association between diuretic and drug use and the development of hyponatremia with higher outdoor temperature; however, others could not find a seasonal variation of diuretic-induced hyponatremia [151]. Diuretics are known to influence water metabolism and lead to a loss of fluid and relatively more electrolytes, especially if drinking is insufficient or if fluids low in electrolytes are consumed [143]. At higher outdoor temperatures the combination of sweating, low fluid and solute intake, or consumption of primarily hypotonic fluids, together with the use of diuretics, may increase the risk of hyponatremia [147].

Primary polydipsia-induced hyponatremia also tends to be more common with higher outdoor temperature, even though this association was not statistically significant. Interestingly, Huwyler et al.

[144] found an association between psychiatric diseases and increased hyponatremia incidence with higher outdoor temperature. Patients with

primary polydipsia, which is typically caused by a psychiatric disorder, may follow a doctor's advice to drink plenty of water and further increase their already excessive (mostly hypotonic) fluid intake during hot weather. Accordingly, they are at risk for water intoxication and hyponatremia, especially when combined with a concomitant stimulus (eg, psychiatric exacerbation, drugs) [48].

Our data showed no clear correlation between relative humidity and hyponatremia. Of note, in Switzerland relative humidity remains nearly constant throughout the year and inversely correlates with outdoor temperature (relative humidity is lowest when outdoor temperature is highest). In tropical regions, the mean monthly outdoor temperature is .23°C, and the humidity is higher compared with Europe [152]. Studies from Asia and northern Australia indicated a higher incidence of hyponatremia during the year and especially during the wet season [140,141,146]. Whether the increased incidence in these regions is caused by increased outdoor temperature or relative humidity has not yet been investigated.

We confirm in the current study that, independent of outdoor temperature or relative humidity, age is significantly correlated to hyponatremia. Aging is associated with a decreased capacity to cope with environmental and disease-related stressors, which influences the sodium and water balance [95,153]. Older adults have a reduced renal function, decreased total body water, and lower renal sodium-conserving ability [154,155]. Additionally, drugs inducing hyponatremia (eg, diuretics and psychotropics) are prescribed more frequently [143], and the aging population suffers more often from cardiovascular and malignant disorders, which influences electrolyte homeostasis [156,157]. Moreover, thirst perception changes with age and often leads to reduced fluid intake, which might be especially important with increased outdoor temperatures [154,158,159]. Along the same lines, malnutrition might play a role as age leads to reduced appetite and thus reduced solute and protein intake, which influences water excretion and the risk of hyponatremia [48,160]. In summary, it seems likely that a combination of these factors is the cause of the described phenomenon.

As shown in other studies, our results suggest that women are more susceptible to hyponatremia than men [137,141]. So far, the reason for this sex difference is unclear. A possible explanation might be the higher expression of aquaporin-2 and a higher sensitivity to endogenous vasopressin in women [161]. With the reduced renal function in age, this may lead to an increased incidence of hyponatremia in women.

Strength and limitations

Some limitations of our study need to be mentioned. First, the study was performed in Switzerland, where outdoor temperature and relative humidity extremes are less common; nevertheless, observing

a correlation between profound hyponatremia and outdoor temperature with a moderate average outdoor temperature supports the hypothesis that outdoor temperature influences the incidence of hyponatremia, but this correlation should be investigated within different and especially hot and humid climate zones.

Additionally, the etiologies of hyponatremia and the comorbidities of cohort A are unknown because data were collected from an electronic registry not indicating this information. Furthermore, we have no objective data on thirst control and the amount of prehospital fluid, salt, and nutrient intake. Cohort B, where the underlying etiology was identified, is small, limiting the power to show a statistically significant association between hyponatremia and outdoor temperature and relative humidity. Furthermore, although our study shows an association, we cannot infer a causal link between outdoor temperature and profound hyponatremia. This study is an exploratory analysis, and thus the findings are hypothesis generating, which should be kept in mind when the results are interpreted.

The main strengths of this study are the large number of investigated patients, the long observation period, and the multicenter design. In contrast to previous smaller studies investigating the seasonal or monthly differences in the incidence of mainly profound hyponatremia and older adults, we studied the mean daily outdoor temperature and the mean daily relative humidity with the incidence of mild and profound hyponatremia over all age groups, providing more detailed insight. Additionally, this study investigated the etiology of hyponatremia in correlation to outdoor temperature and relative humidity in a prospective way.

In summary, our data show that higher outdoor temperature is associated with an increased incidence of profound hyponatremia, whereas mild hyponatremia is not. Relative humidity seems not to be associated with the incidence of hyponatremia. Diuretic-induced hyponatremia is more commonly seen with higher outdoor temperatures, whereas the distribution of other hyponatremia etiologies is equally distributed. Our data indicate that diuretics should be used with caution during hot weather and especially in older adults and women, who are more susceptible to developing hyponatremia.

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Clinical trial information

ClinicalTrials.gov no. NCT01456533 (registered 20 October 2011).

Disclosure summary

The authors have nothing to disclose.

Manuscript III: Seasonality of hypoosmolar hyponatremia in medical inpatients - data from a nationwide cohort study

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Abstract

Context: Hyponatremia is the most prevalent electrolyte disturbance in hospitalized patients. Previous studies have shown a seasonal variation of profound hyponatremia with higher prevalence during warmer months.

Objective: This study aimed at analyzing the seasonal prevalence, sex and age-specific differences of hyponatremia in medical inpatients.

Design: Nationwide cohort study from January 2009 and December 2015 using prospective administrative data.

Setting: Medical inpatients.

Patients: Diagnosis of hypoosmolar hyponatremia.

Main outcome measures: The primary outcome was the monthly alteration in hyponatremia prevalence. Secondary outcomes were the association of outdoor temperature with hyponatremia prevalence and differences among sex and age groups.

Results: Of 2,426,722 medical inpatients, 84,210 were diagnosed with hypoosmolar hyponatremia, of whom 61% (n=51,262) were female. The highest overall prevalence of hyponatremia was observed in July (4.5%, n=8,976), it was lowest in December (2.7%, n=6,530). The overall prevalence of hyponatremia in women compared to men was higher by 58% (OR 1.58 [95% CI 1.56 to 1.60]). The sex-specific difference was most pronounced in the warmest month of July (mean temperature 20.1°C, OR 1.76 [95% CI 1.68 to 1.84]). We observed the strongest association between seasonality and hyponatremia in elderly (>80 years) female inpatients admitted during the month of July (OR 2.40 [95% CI 2.20 to 2.62]).

Conclusion The prevalence of diagnosed hypoosmolar hyponatremia in medical inpatients increases during summer months with higher outdoor temperature. Elderly female inpatients were most susceptible to the seasonal rise in hyponatremia prevalence.

Introduction

Hyponatremia is the most prevalent electrolyte disbalance affecting 10-15% of hospitalized patients and is associated with a poor clinical outcome [58,135,137,138]. Predisposing risk factors for hyponatremia are disease stress-related drive of arginine vasopressin [162,163], heart failure, liver cirrhosis or renal failure causing volume-overload, dehydration with sodium loss (e.g. infection), and medications (e.g. diuretics and antidepressant). A meta-analysis of 81 studies including 147,948 participants found that already mild hyponatremia is significantly associated with overall mortality [164] and is associated with a worse prognosis in multimorbid patients, e.g. disease of the liver, heart, kidney, brain and lungs [165–168]. Importantly, in-hospital health care providers are frequently faced with this burdensome electrolyte disorder and a season-dependent variation may alter in-hospital resource allocation accordingly.

A season-dependent variation in the hyponatremia prevalence has recently been described in the emergency department setting [49,144–146]. In particular, the prevalence of profound hyponatremia has been associated with outdoor temperature and has been shown to be increased during summer months [49,145]. However, these studies focus on patients in the emergency department and information on medical inpatients are scarce. Thus, large scale data are needed not only to validate previous findings from the emergency department setting but also to identify nationwide epidemiological variations within hyponatremic medical inpatients. Furthermore, previous studies suggest that women and elderly patients are more susceptible towards developing hyponatremia [49,141,145,169,170]. However, whether these associations alter throughout the year with changing outdoor temperature is poorly explored [49,145].

Therefore, the aim of this study was to investigate in-hospital hyponatremia prevalence throughout the year stratified for sex and age groups.

Materials and Methods

Participants, Data Sources, and Study Variables

In this nationwide cohort study, we performed a cross-sectional analysis using prospective administrative data from January 1, 2009 to December 31, 2015 provided by the Swiss Federal Statistical Office.

The database includes all Swiss hospitalization records from acute care, general, and specialty hospitals, excluding hospital units of post–acute care institutions. Non-medical, psychiatric, and nonadult (<18 years of age) patients were excluded from the final analysis. Medical cases were defined as encoded by the Federal Statistical Office. Thus, gynecology and obstetrics, pediatrics, ophthalmology, intensive care, otolaryngology, surgery, psychiatry, dermatology and venerology, radiology, geriatrics, rehabilitation and emergency-center patient records were excluded.

To qualify for inclusion in this study cohort, hospitalized patients had a primary or secondary discharge record of hypoosmolar hyponatremia diagnosis according to the International Classification of Diseases, 10th Revision German Version (ICD-10-GM): E87.1 (hypoosmolar hyponatremia) or E22.2 (syndrome of inappropriate antidiuresis), respectively. Patients without clear diagnosis of hyponatremia were not included in the analysis.

Data on mean daily outdoor temperature were gathered from the open data repository of the Federal Office of Meteorology and Climatology MeteoSwiss (Bundesamt fuer Meteorologie und Klimatologie MeteoSchweiz).

The institutional review board of Northwestern and Central Switzerland approved of this study and waived patients' informed consent owing to the use of deidentified data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [171].

Outcomes

The primary outcome was the monthly alteration in hypoosmolar hyponatremia prevalence among medical inpatients. Secondary outcomes were sex and age specific monthly variations in hypoosmolar hyponatremia prevalence in these patients. Outcome measures were mean monthly odds ratio of hypoosmolar hyponatremia diagnosis and mean monthly outdoor temperature.

Statistical analysis

Unless stated otherwise, categorical variables are expressed as number (percentage) and continuous variables as mean (standard deviation, SD). Subgroup analyses were performed for sex (male, female) and for pre-defined age groups (based on quartiles of all hospitalized patients: ≤55 years, 56 to 70 years, 71 to 80 years and >80 years). Furthermore, sensitivity analyses were performed for the

diagnoses of hypoosmolar hyponatremia (E87.1) and syndrome of inappropriate antidiuresis (E22.2) separately.

We used univariable and multivariable logistic regression models to calculate odds ratio (OR) and 95% confidence intervals (CI) for the hypoosmolar hyponatremia diagnosis. The multivariable models were adjusted for age, nationality, hospital teaching status, type and date (month and year) of admission, disease severity score (Charlson Comorbidity Index), type of admission (planned versus unplanned), and main comorbidities. Monthly prevalence rates were calculated and compared among the predefined sex and age subgroups.

The significance level was set as $\alpha = 5\%$. All p-values are two-sided and have not been adjusted for multiple testing. Statistical analyses were performed using Stata 15.1 (StataCorp. 2015. College Station, TX, USA: StataCorp LP).

Results

Baseline characteristics

Of 2,426,722 medical inpatients included in this study, 84,210 (3.5%) were diagnosed with hypoosmolar hyponatremia, of whom 51,262 (61%) were female. Among inpatients with a diagnosis of hypoosmolar hyponatremia, the majority was admitted through the emergency department and around 88% were community-dwelling. Patients with hypoosmolar hyponatremia had a high burden of comorbidities such as heart failure, chronic kidney disease, pneumonia, and liver failure. The mean [SD] Charlson Comorbidity Index was significantly higher in patients diagnosed with hypoosmolar hyponatremia as compared to medical controls at the same time of hospitalization (1.9 [2.6] vs. 1.5 [2.3], p-value < 0.001) (**Table 1**)**.**

Table 1 Baseline Characteristics

	Hyponatremia	Medical controls	p-value
Socio-demographics			
Hospitalizations, n	84`210	234`2512	
Sex, female, n (%)	51`262 (60.9)	1`114`006 (47.6)	<0.001
Age groups, n (%)			<0.001
<56 years	10`713 (12.7)	584`615 (25.0)	
56 to 70 years	21`620 (25.7)	627`761 (26.8)	
71 to 80 years	23`094 (27.4)	565`363 (24.1)	
>80 years	28`783 (34.2)	564`773 (24.1)	
Swiss residents, n (%)	74`796 (88.8)	1`940`162 (82.8)	<0.001
Hospital teaching level, n (%)			
Tertiary care hospital	55`162 (65.5)	1`535`222 (65.5)	0.85
Hospital admission			<0.001
Emergency admission	73`718 (87.5)	1`647`354 (70.3)	
Elective admission	9`687 (11.5)	662`611 (28.3)	
Others	805 (1.0)	32`547 (1.4)	
Living situation, n (%)			
Before admission			
At home	73`880 (87.7)	2`041`444 (87.1)	<0.001
Comorbidities, n (%)			
Diabetes mellitus	15`227 (18.1)	366`271 (15.6)	<0.001
Arterial hypertension	45`795 (54.4)	916`926 (39.1)	<0.001
Coronary artery disease	12`770 (15.2)	497`689 (21.2)	<0.001
Cerebrovascular disease	4`646 (5.5)	153`786 (6.6)	<0.001
Heart failure	20`255 (24.1)	426`973 (18.2)	<0.001
Cancer	14`507 (17.2)	337`744 (14.4)	<0.001
Chronic kidney disease	22`249 (26.4)	408`818 (17.5)	<0.001
Chronic obstructive pulmonary disease	11`418 (13.6)	226`501 (9.7)	<0.001
Pneumonia	10`694 (12.7)	177`656 (7.6)	<0.001
Liver failure	6`707 (8.0)	79`419 (3.4)	<0.001
Severity index, mean (SD)			
Charlson Comorbidity Index	1.9 (2.6)	1.5 (2.3)	<0.001

COPD, Chronic obstructive pulmonary disease; n, number; SD, standard deviation.

Seasonal variation of hypoosmolar hyponatremia

We found a strong seasonal variation in the prevalence of hypoosmolar hyponatremia (R^2 = 0.56, p-values = 0.005). While the highest overall prevalence of hypoosmolar hyponatremia was noted in the month of July (n=8,976, 4.5%), it was lowest in the month of December (n=6,530, 2.7%). We observed a gradual increase in hypoosmolar hyponatremia from the month of January to the month of July, followed by a gradual decrease thereafter. This was paralleled with a gradual increase in mean monthly outdoor temperature from the months of January to the month of July with a mean [SD] monthly outdoor temperature in January of 1.4°C [1.6] to July of 20°C [1.8] and followed by a continued decrease in mean monthly outdoor temperature, respectively (**Table 2, Figure 1**)**.** In the sensitivity analyses for the respective diagnosis of hypoosmolar hyponatremia (E87.1) and syndrome of inappropriate antidiuresis (E22.2), there were no significant differences in the temporal dynamics throughout the year (**Figure 2 A and B**).

Table 2 Mean monthly outdoor temperature and prevalence of hyponatremia among hospitalized male and female patients

Month of hospital admission	Outdoor temperature (C°), mean (SD)	Total prevalence of hyponatremia, n (%)	Prevalence of hyponatremia in male patients, n (%)	Prevalence of hyponatremia in female patients, n (%)
January	1.4 (1.6)	6`747 (3.2)	2`688 (2.4)	4`059 (4.0)
February	1.3 (2.1)	6`262 (3.2)	2`547 (2.5)	3`715 (4.0)
March	6.5 (1.5)	6`787 (3.2)	2`691 (2.5)	4`096 (4.1)
April	11.1 (1.2)	6`407 (3.3)	2`597 (2.6)	3`810 (4.1)
May	14.3 (1.6)	6`541 (3.4)	2`520 (2.5)	4`021 (4.3)
June	18.0 (0.7)	7`309 (3.8)	2`886 (2.9)	4`423 (4.8)
July	20.1 (1.8)	8`976 (4.5)	3`182 (3.1)	5`794 (6.1)
August	19.6 (1.2)	8`212 (4.3)	3`126 (3.1)	5`086 (5.5)
September	15.5 (1.1)	7`116 (3.7)	2`720 (2.7)	4`396 (4.7)
October	11.0 (1.2)	6`928 (3.5)	2`763 (2.7)	4`165 (4.3)
November	6.6 (1.0)	6`395 (3.2)	2`602 (2.5)	3`793 (4.0)
December	2.6 (1.4)	6`530 (2.7)	2`626 (2.1)	3`904 (3.4)

C°, degrees Celsius; n, number; SD, standard deviation

Figure 1: Association of hyponatremia in hospitalized patients, month of admission, sex, and stratified by age groups.

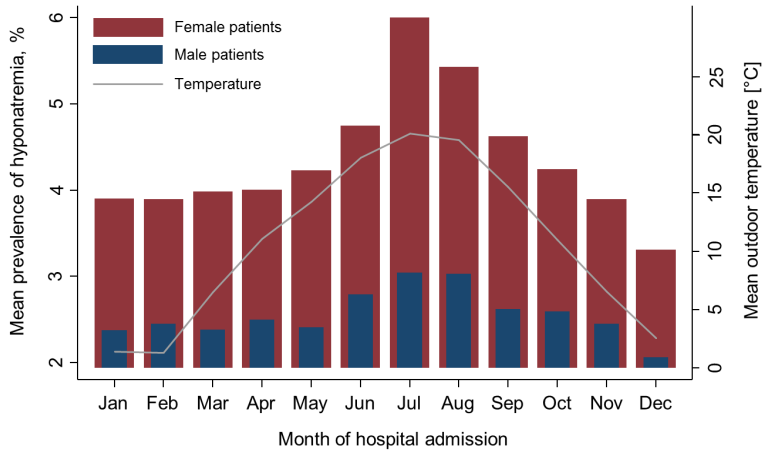
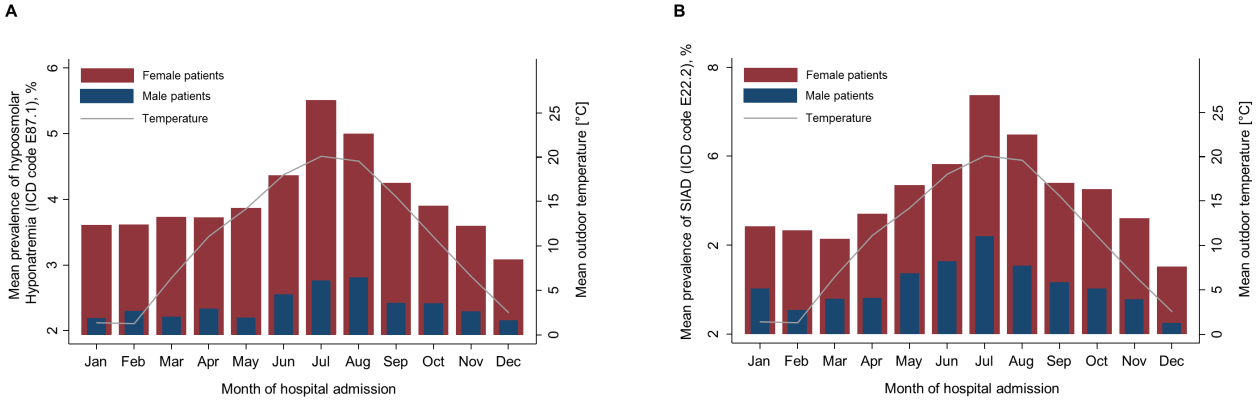


Figure 2: Mean monthly prevalence of hyponatremia stratified for sex



Seasonal variation of hypoosmolar hyponatremia stratified by sex and age categories

The overall prevalence of hypoosmolar hyponatremia was higher in women as compared to men (OR 1.72 [95%-CI 1.69 to 1.74], p<0.001). This remained statistically significant when adjusting for comorbidities such as heart failure, chronic kidney disease, pneumonia and liver failure (OR 1.58 [95%-CI 1.56 to 1.60], p<0.001) (**Table 3**). Sex-specific differences in hypoosmolar hyponatremia increased in parallel with the mean monthly outdoor temperature (**Figure 1)**. While in January 2.4% men and 4% women were diagnosed with hypoosmolar hyponatremia (OR 1.54 [95%-CI 1.46 to 1.62], p<0.001), 3.1% men and 6.1% women were diagnosed with hypoosmolar hyponatremia in July (OR 1.76 [95%-CI 1.68 to 1.84]) (**Tables 2 and 3**).

The in-hospital prevalence of hypoosmolar hyponatremia increased with increasing age. The overall prevalence of hypoosmolar hyponatremia for patients <56 years was 1.8% and increased for the age rage 56 to 70 years to 3.3% and for the age range 70 to 80 years to 3.9% and was 4.9% for patients >80 years (data not shown separately) (**Figure 3**).

Whereas the overall prevalence of hyponatremia was higher in women as compared to men, we did not find such a significant difference after stratification for month. In older patients, however, we did observe month-stratified differences in the prevalence of hypoosmolar hyponatremia in hospitalized medical patients (**Table 3**). These associations are visualized in **Figure 3**. Based on terms of interaction we found age to be a strong effect modifier in the association between sex and the prevalence of in-hospital hyponatremia.

To exclude that these findings are due to an increased admission rate of female and elderly patients during summer months, we investigated the monthly admission rate of these patients and found that there was no seasonal difference in admission rates throughout the year (data not shown).

Figure 3: Mean monthly prevalence of (A) hypoosmolar hyponatremia (ICD code E87.1) and (B) syndrome of inappropriate antidiuresis (ICD code E22.2) stratified for sex

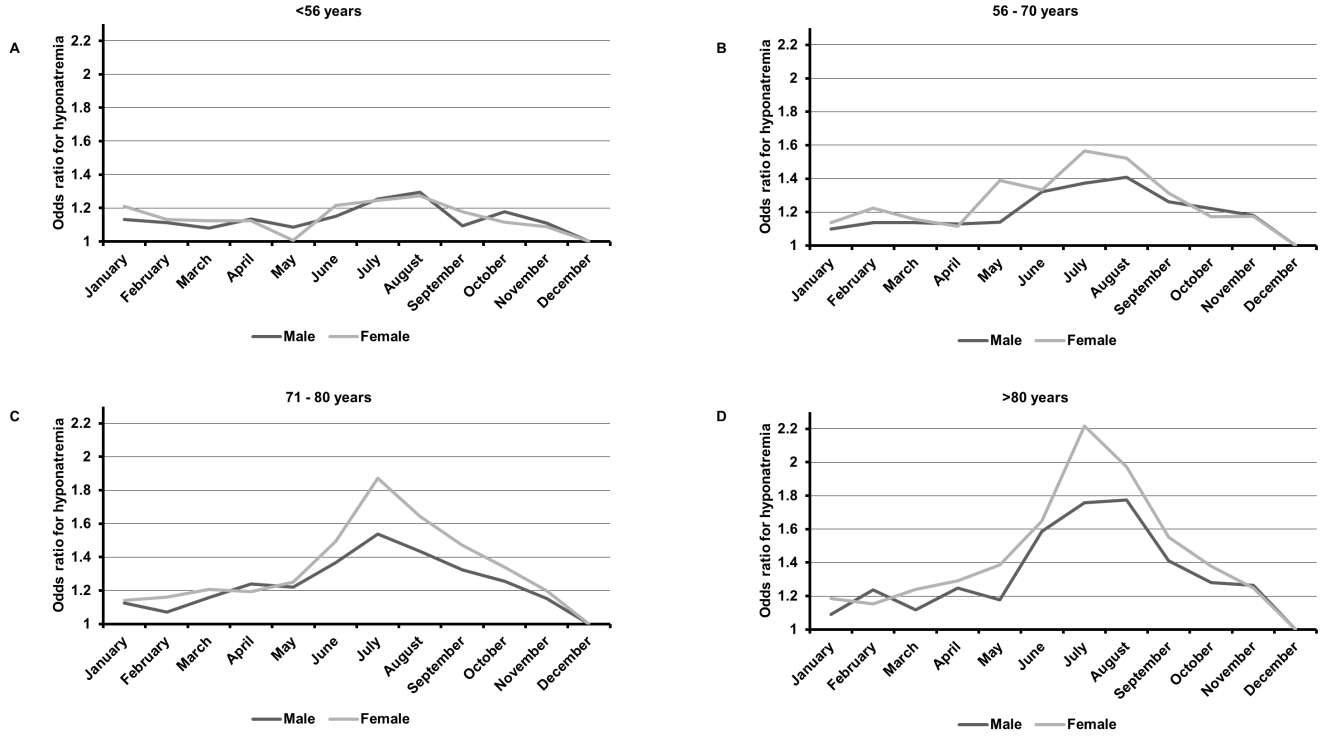


Table 3 Association of monthly-stratified hyponatremia in hospitalized patients among sex and age groups

	Overall		<56 years		56 to 70 years		71 to 80 years		>80 years	
	Adjusted OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Overall										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.58 (1.56-1.60)	<0.001	1.04 (1.00-1.09)	0.035	1.24 (1.20-1.27)	<0.001	1.78 (1.73-1.83)	<0.001	2.14 (2.08-2.21)	<0.001
January										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.54 (1.46-1.62)	<0.001	1.09 (0.96-1.24)	0.197	1.21 (1.10-1.34)	<0.001	1.69 (1.53-1.87)	<0.001	2.21 (1.99-2.44)	<0.001
February										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.51 (1.43-1.59)	<0.001	1.04 (0.90-1.20)	0.583	1.26 (1.14-1.39)	<0.001	1.78 (1.60-1.98)	<0.001	1.91 (1.73-2.11)	<0.001
March										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.54 (1.47-1.62)	<0.001	1.07 (0.93-1.27)	0.341	1.19 (1.08-1.31)	0.001	1.73 (1.58-1.91)	<0.001	2.17 (1.96-2.40)	<0.001
April										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.49 (1.41-1.57)	<0.001	1.02 (0.86-1.17)	0.790	1.17 (1.06-1.30)	0.002	1.61 (1.45-1.78)	<0.001	2.06 (1.86-2.28)	<0.001
May										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.63 (1.55-1.72)	<0.001	0.94 (0.82-1.09)	0.420	1.46 (1.32-1.61)	<0.001	1.71 (1.55-1.89)	<0.001	2.30 (2.07-2.55)	<0.001
June										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.57 (1.50-1.65)	<0.001	1.09 (0.95-1.25)	0.220	1.18 (1.08-1.30)	0.001	1.82 (1.66-2.01)	<0.001	2.06 (1.88-2.27)	<0.001

	Overall		<56 years		56 to 70 years		71 to 80 years		>80 years	
	Adjusted OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**
July										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.76 (1.68-1.84)	<0.001	1.05 (0.92-1.19)	0.508	1.33 (1.22-1.46)	<0.001	1.98 (1.81-2.16)	<0.001	2.40 (2.20-2.62)	<0.001
August										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.64 (1.57-1.72)	<0.001	1.04 (0.91-1.18)	0.568	1.29 (1.17-1.41)	<0.001	1.87 (1.71-2.05)	<0.001	2.17 (1.99-2.37)	<0.001
September										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.62 (1.54-1.70)	<0.001	1.13 (0.99-1.30)	0.075	1.24 (1.12-1.37)	<0.001	1.81 (1.64-1.99)	<0.001	2.16 (1.96-2.38)	<0.001
October										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.52 (1.44-1.60)	<0.001	0.97 (0.85-1.11)	0.648	1.12 (1.01-1.23)	0.030	1.77 (1.61-1.95)	<0.001	2.15 (1.95-2.38)	<0.001
November										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.48 (1.40-1.56)	<0.001	1.04 (0.90-1.20)	0.594	1.17 (1.06-1.29)	0.002	1.68 (1.52-1.86)	<0.001	1.94 (1.75-2.15)	<0.001
December										
Male patients	reference		reference		reference		reference		reference	
Female patients	1.57 (1.49-1.66)	<0.001	1.05 (0.91-1.21)	0.487	1.21 (1.10-1.34)	<0.001	1.78 (1.61-1.96)	<0.001	2.08 (1.88-2.30)	<0.001

OR, odds ratio; CI, confidence interval

Discussion

Key findings of this study are threefold: First, the prevalence of hyponatremia in medical inpatients increases during summer months and is strongly associated with warmer outdoor temperature. Second, hyponatremia was more common in women, especially during summer months. Third, increasing age was associated with a higher in-hospital prevalence of hyponatremia, and again, this finding was most pronounced during summer months.

Our nationwide cohort data conclusively confirm a seasonal variation of the prevalence of hyponatremia being highest during summer months [49,144,145]. While previous studies investigated smaller patient numbers or focused on emergency department setting, the present study expands the findings to a large medical inpatient population. The overall prevalence of hypoosmolar hyponatremia in hospitalized patients of 3.5% is lower as compared to 10-15% prevalence reported in previous studies [58,135,137,138]. This could possibly be due to an underreporting of hyponatremia and that our data represent the more profound and symptomatic cases of hyponatremia. This would in fact be in line with data from the outpatient setting that indicated a season dependent effect in particular for patients with profound hyponatremia [49,145].

Reasons for the increased prevalence of hyponatremia during summer months with increased outdoor temperature may be attributed to several predisposing factors. Our data suggest that hypoosmolar hyponatremia overall as well as syndrome of inappropriate antidiuresis taken as single diagnosis increase in parallel during summer months. Hypoosmolar hyponatremia may be caused by diuretic-induced hyponatremia, primary polydipsia, or volume overload due to heart or renal failure, respectively. Even though our data cannot differentiate between the different hypoosmolar hyponatremia etiologies, previous studies have described increased diuretic-induced hyponatremia during summer months [49,172]. The pathophysiological reasoning is that diuretics lead to a relative renal salt loss and when combined with dehydration, as during months with higher outdoor temperature, hyponatremia might develop. With regard to hyponatremia caused by heart or renal failure, studies suggest that they are more commonly decompensated and thus of a higher severity during summer months which could as well lead to hyponatremia [173]. The distribution of hyponatremia prevalence due to the syndrome of inappropriate antidiuresis increases according to our results during summer months. A hypothetical explanation is that increased outdoor temperature is a stimulus for arginine vasopressin. We speculate that in combination with increased fluid intake this might lead to hyponatremia, especially when consuming hypotonic fluids [48,49,174]. Additionally, idiopathic syndrome of inappropriate antidiuresis, especially in the elderly, could be increased during summer months but further prospective studies are needed to validate this hypothesis.

As known from previous studies, women tend to have a higher prevalence of hyponatremia in general [49,137]. Our results are in line with those findings, suggesting that women are prone to develop

hyponatremia [145]. Interestingly, we show that this effect is highest with higher outdoor temperature. It is possible that the increased outdoor temperature influences sex hormones differently, making women more susceptible to develop hyponatremia during increased outdoor temperatures. It was shown that estrogen affects aquaporin-4 expression regulating water homeostasis [175] and that aquaporin-2 expression is higher and more sensitive to endogenous arginine vasopressin in women [176]. Lastly, it is speculated that women tend to drink generally more fluids than men and primary polydipsia is also more common in women [17,47,48]. This might lead to a volume overload and relative salt deficit, especially when renal function is impaired, and may result in hyponatremia [48].

Ageing has been described as independent risk factor for electrolyte disturbances, especially hyponatremia [141]. We here confirm that ageing is associated with an increased prevalence of hyponatremia and show that this effect is also more pronounced with higher outdoor temperature. Ageing is associated with maladaptation to stress and decreased capacity to cope with environmental, disease-related, and iatrogenic stress [153,177]. Common factors predisposing hyponatremia in the elderly are an impaired renal function, increased consumption of hyponatremia-inducing drugs (e.g., diuretics and psychotropics), increased occurrence of cardiac and pulmonary diseases and increased idiopathic syndrome of inappropriate antidiuresis which all influence the water homeostasis [143,154–157]. Our results indicate that patients with hyponatremia had higher rates of cardiac and pulmonary diseases. Additionally, it has been shown that thirst perception is decreased with age [154,158,159]. It could therefore be that the reduced thirst perception in the elderly in combination with medication and fluid loss (e.g., sweating, vomitus, diarrhea) results in dehydration hyponatremia, especially during higher outdoor temperature.

These data will have to be interpreted in the context of the study design. First, using administrative data is prone to confounding due to the risk of misclassification and underreporting of hyponatremia and lack of validating diagnosis with laboratory measurements. In fact, merely 3.5% of all included hospitalized patients were diagnosed with hyponatremia, although evidence suggests a much higher prevalence in hospitalized patients [135]. We expect our data to still be representable as rate of ascertainment is expected to be constant throughout the year. Second, our data do not differentiate between hyponatremia on admission versus hospital-acquired hyponatremia. ICD-10 coding is generally done at the time of discharge or death. Consequently, some of the patients may have developed hyponatremia during hospitalization, rather than on admission. Assuming a constant rate of hospital-acquired hyponatremia throughout the year, the observed seasonal variation would however be explained by varying hyponatremia prevalence on admission. Our data are based on hospital claims data of ICD coded diagnoses “hypoosmolar hyponatremia” and “syndrome of inappropriate antidiuresis”, but exact laboratory measurements were not available. Third, the non-

experimental design of our study limits the ability to draw causal links between the prevalence of hyponatremia, seasonality, sex- and age-specific variations. Fourth, since we do not have information on clinical symptoms and severity of hyponatremia, we are unable to account for unmeasured (and unmeasurable) residual confounding (e.g., etiology of hyponatremia, thirst perception, volume status). However, our study has several strengths: the large nationwide data, the high representability, and the long study period. All analyses were adjusted for multiple comorbidities and possible confounders. Furthermore, this is the first study to date focusing on medical inpatients and thus provides information about a patient population which has been poorly studied so far.

In conclusion, in medical inpatients, hyponatremia is increased during summer months with higher outdoor temperature. Female and elderly are at higher risk to develop hyponatremia and this effect is enforced during summer months.

Declaration of interest

The authors have no conflict of interest.

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Manuscript IV: Glucagon-like peptide-1 receptor agonists: new treatment option for patients with primary polydipsia?

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Abstract

Background Primary polydipsia is part of the polyuria-polydipsia syndrome and characterized by increased fluid intake. Excessive fluid may lead to complications such as hyponatremia. However, besides behavioral therapy, treatment options are scarce. Glucagon-like peptide-1 (GLP-1) receptor agonists reduce appetite and energy intake and could play a role in drinking and water homeostasis. The purpose of this study was to investigate whether GLP-1 receptor agonists reduce fluid intake in patients with primary polydipsia.

Method In this three-week double-blind, placebo-controlled, randomized, cross-over trial, 34 patients with primary polydipsia received weekly dulaglutide (Trulicity®) 1.5mg and placebo (0.9% sodium chloride). During the third week, patients attended an 8-hour evaluation visit with free water access. The primary endpoint was total fluid intake during the evaluation visit. The treatment effect was estimated using a mixed-effects model, accounting for treatment sequence and patient.

Results Median [IQR] age of participants (23 (67.6%) female) was 29.5 years [26.0, 38.8]. We found that median [IQR] total fluid intake was lower in patients treated with dulaglutide as compared to placebo: 2250 ml [1600-2600] versus 2400 ml [1850-3400]. Two third of patients on dulaglutide had a reduced fluid intake by -453 ml [95% CI -851, -54], p=0.033, corresponding to a 15% relative reduction. Thirst perception was slightly reduced in patients receiving dulaglutide, and electrolytes were similar between the two groups at the beginning of the evaluation visit.

Conclusion This study suggests that GLP-1 receptor agonists reduce fluid intake in patients with primary polydipsia and could therefore be a new treatment option for these patients.

Introduction

Primary polydipsia is characterized by excess water intake and consecutive excretion of profound quantities of dilute urine [14,28]. This disorder has most often been described in psychiatric patients (psychogenic polydipsia) but can also be seen in subjects with a defective thirst mechanism or health conscious people with voluntary increased fluid intake (habitual polydipsia) [13,14,47,178]. In contrast to the common believe, increased fluid intake is not without complication but may lead to hyponatremia with symptoms such as nausea, falls, seizures and even death [48]. However, treatment options for primary polydipsia are scarce. While voluntary fluid reduction would be the ideal treatment, it is often unsuccessful because of continuous thirst and compulsive drinking behavior [29,33,118]. Some medications have been studied to improve polydipsic behavior such as olanzapine, lithium, aripiprazole and clozapine [36,38–40,42]. These drugs are mainly used to treat psychotic symptoms and in schizophrenic patients and might therefore reduce polydipsic behavior in these patients. However, they have unfavorable side effects such as weight gain and type 2 diabetes and are therefore no suitable option for otherwise healthy people with primary polydipsia. A medication with primarily thirst reducing action would be desirable.

The hormone glucagon-like peptide-1 (GLP-1) is released in response to food intake [179,180] and is involved in the regulation of appetite and energy intake [179,181–184]. GLP-1 receptor agonists are widely used for the treatment of type 2 diabetes mellitus and weight management in obese patients [185]. These satiating properties make GLP-1 and its receptor agonists an interesting therapeutic target in the regulation of thirst and drinking. Studies investigating GLP-1 receptor agonists on food intake revealed a concomitant reduction of fluid intake both in humans and rats in the presence and absence of food [186,187].

The aim of this study was therefore to investigate whether GLP-1 receptor agonists as compared to placebo reduce fluid intake and thirst perception in patients with primary polydipsia.

Materials and methods

Study design and participants

This is a single center, randomized, double blind, placebo controlled, 3-week crossover trial in 34 patients with primary polydipsia. The trial was conducted at the University Hospital Basel, Switzerland. Inclusion criteria were age between 18 and 65 years, polyuria > 50 ml/kg body weight per day and polydipsia of > 3 liters per day. Exclusion criteria were central or nephrogenic diabetes insipidus, secondary polyuria (e.g., diabetes mellitus, hypokalemia, hypercalcemia), history of pancreatitis and previous treatment with GLP-1 receptor agonists within the last 3 months. The study protocol and study medication were approved by both the local ethic committee and the national agency for the authorization and supervision of therapeutic products (Swissmedic). Written informed consent has been obtained from each participant after full explanation of the purpose and nature of all procedures used. The study was registered on ClinicalTrials.gov (NCT02770885).

Study objective and outcomes

The objective of this study was to explore whether a three-week treatment with GLP-1 receptor agonist dulaglutide (Trulicity®) as compared to placebo reduces fluid intake in patients with primary polydipsia. The primary outcome was total fluid intake (ml) during an 8-hour evaluation visit.

Further outcomes were thirst perception during the preceding week and during the evaluation visit, 24-hour urine output during the evaluation visit and the following 16 hours, day and nighttime urinary frequency, quality of life, serum and urine electrolytes and osmolality, and adverse effects e.g. gastrointestinal symptoms.

Study intervention

The procedures and timeline of the study are schematically displayed in figure 1.

All study participants received in random order a 3-week treatment with either dulaglutide (Trulicity®) 1.5 mg or placebo (0,9% sodium chloride) subcutaneously once weekly. After a wash-out period of at least 3 weeks, participants received the complementary treatment.

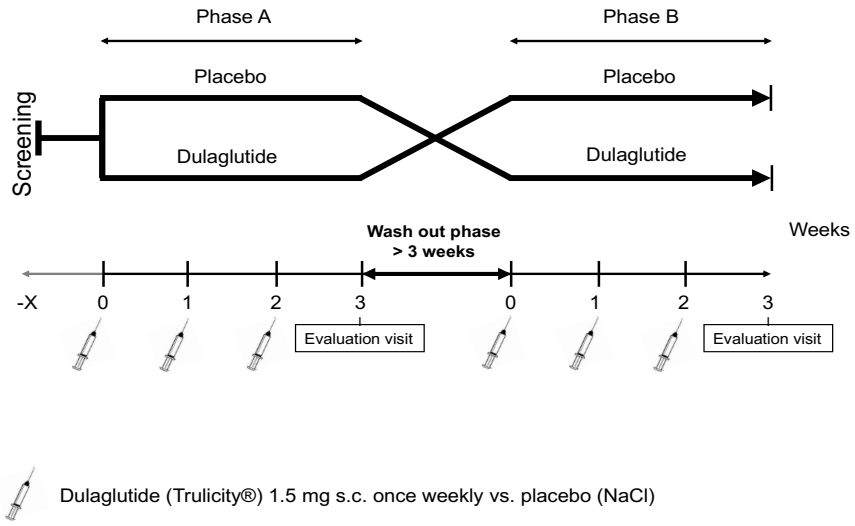

Figure 1: Flow Chart

Assessment of fluid intake and urinary output

Patients attended an 8-hour evaluation visit (8 am to 4 pm) at the study site after an overnight fast (no food and drinks) for 12 hours within 7 days following the third study drug injection. At arrival, participants were requested to void their bladders and a 24-hours urine collection was started. Clinical parameters, symptoms and adverse effects were assessed at 8 am, noon and 4 pm. Symptoms and adverse effects (thirst, hunger, nausea, abdominal pain) were assessed using the a 10-point numerous rating scale (e.g., 0 = no thirst, 10 = extreme thirst).

At 8.30 am (breakfast) and at noon (lunch) standardized, savory meals were served (consisting of 116g carbohydrates, 60g fat, 25g proteins, 12g fibers, 5.7g salt and 1284kcal in total). To control for food intake, participants were requested to consume the entire meals on both evaluation visits, irrespective of their appetite. Starting at 8.30 am, a water dispenser with a content of 10 liters was provided and refilled if necessary. The amount of water in the dispenser was unknown to the participants. Participants were invited to drink freely from the dispenser during the evaluation visit. Besides the provided meals and water no other food or drinks were allowed. At 4 pm, participants were asked to void their bladders and instructed to collect their urine until 8 am the following day.

Assessment of polydipsic behavior

Thirst perception was assessed in different ways during our study: First, we assessed thirst perception at each study visit using a 10-point numerous rating scale. Patients were asked to indicate their average thirst perception during the preceding week. Second, at the evaluation visit, patients were asked at 8

am, noon, 1pm and 4 pm to indicate their current thirst perception. Furthermore, at the weekly visits, reported average daily fluid intake during the day, emictions per day and at night were assessed.

Assessment of quality of life

We assessed quality of life in our patients in two ways: First, patients were asked to rate their perceived reduced quality of life by the polyuria-polydipsia symptoms on a 10-point rating scale during the preceding week (e.g., 0 = quality of life not reduced, 10 = quality of life maximally reduced). Second, patients answered the standardized short form 12 (SF-12) questionnaire (Quelle), a standardized questionnaire to assess quality of life, at each study visit.

Assessment of electrolytes

At the screening visit, patients had a basal blood draw for serum electrolytes and osmolality, serum glucose, urinary electrolytes and osmolality. At the beginning of the 8-hour the evaluation visits an intravenous line was placed into the antecubital vein for blood sampling. Blood and urine samples were collected at 8 am, noon and 4 pm for the measurement of the above-mentioned laboratory values.

Assessment of adverse effects

At every weekly visit and during the evaluation visit, gastrointestinal symptoms, e.g. nausea, abdominal pain, and diarrhea were assessed on a 10-point numerous rating scale (e.g., 0 = no nausea, 10 = unbearable nausea). Other adverse effects were recorded free text.

Statistical analysis

For the analysis of the primary endpoint, total water intake during the evaluation visit, a linear mixed-effect model was used. The model included study arm, sequence and their interaction term as predictors (fixed effects). Further, a random intercept was fitted for patient (random effect). Model residual distribution was inspected visually. 95% confidence intervals were computed using the profile method. P-values were calculated using the Satterwaite's method for deriving degrees of freedom and t-statistics (implemented in the R package lmerTest). The estimated difference in the primary endpoint between dulaglutide and placebo is indicated with 95% confidence interval and interpreted regarding its clinical relevance and regarding the assumed effect for sample size estimation (13% reduction of dulaglutide versus placebo). As sensitivity analysis, the primary analysis was repeated on the per protocol set and including adverse effects at the beginning and at any time-point during the evaluation visit.

All secondary analyses in this study are exploratory and hypothesis generating. These tests of secondary outcomes all explore the general prediction that dulaglutide has hypodipsic properties. For all outcomes, descriptive summary statistics are reported for dulaglutide and placebo separately for each measurement time. For continuous variables the median and interquartile range is reported. Analysis were performed using the statistic program R [188].

Results

Baseline characteristics

The 34 included patients (67.6% female) had a median [IQR] age of 29.5 years [26.0, 38.8] and had a median [IQR] body mass index of 23.1 kg/m^2 [20.7, 25.5]. At baseline, median [IQR] reported fluid intake was 4500 ml per day [3600, 5000] and median [IQR] 24h urine output was 4700 ml [3900, 5600]. Baseline characteristics are shown in Table 1.

Table 1: Baseline Characteristics and polydipsic behavior

Baseline characteristics	**34**
Age (years), median (IQR)	29.5 (26.0, 38.8)
Male gender, n (%)	11 (32.4)
BMI (kg/m^2), median (IQR)	23.1 (20.7, 25.5)
Psychiatric comorbidities, n (%)	20 (58.8)
Other comorbidities, n (%)	14 (41.2)
Smoking, n (%)	14 (41.2)
Polydipsic behavior	
Reported daily fluid intake (ml), median (IQR)	4500 (3600, 5000)
24h urine output (ml), median (IQR)	4700 (3900, 5600)
Time since onset of symptoms (months), median (IQR)	120.0 (61.0, 120.0)

Fluid intake and 24-hour urine output

Median [IQR] fluid intake during the 8-hour evaluation visit was lower on dulaglutide as compared to placebo treatment: 2250 ml [1600, 7400] versus 2400 ml [1850, 3400]), see Figure 2. The median [95%-confidence interval] difference of fluid intake on dulaglutide compared to placebo treatment was -453 ml [-851, -54] (p-value = 0.033), which correspond to a fluid reduction of 15%. Two third of participants drank less on dulaglutide than on placebo treatment as illustrated in the histogram (Figure 3). The sensitivity analyses confirmed these findings.

24-hour urine output tended to be lower in patients treated with dulaglutide, median [IQR] 3250 ml [2288, 4362] compared to placebo, median [IQR] 4150 ml [3262, 5788]. The median [IQR] difference of urine output on dulaglutide compared to placebo treatment was -675 ml [-1391, 41] (p = 0.074).

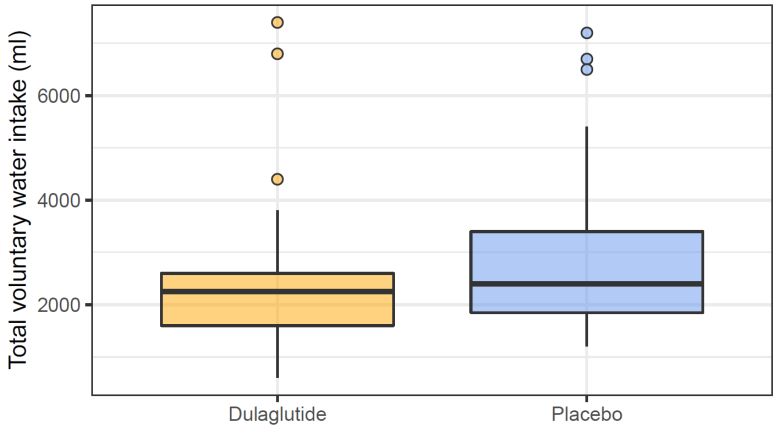

Figure 2: Total voluntary water intake within 8 hours at the evaluation visit after treatment with placebo or dulaglutide.

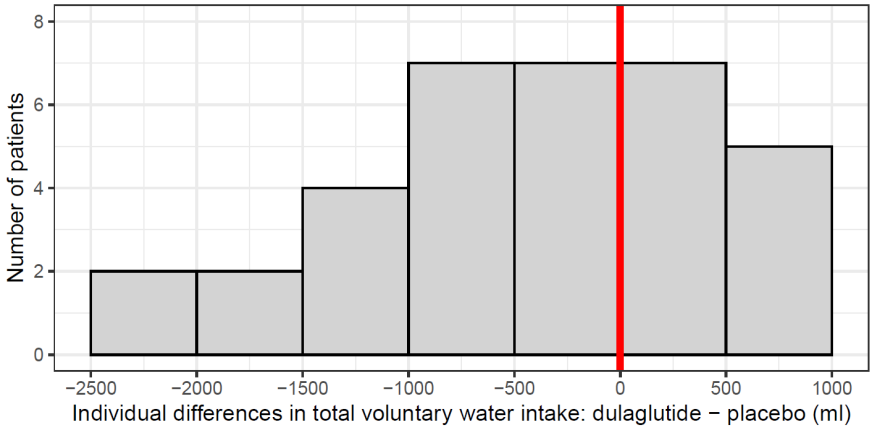

Figure 3: Within-patient differences in total voluntary water intake within 8 hours at the evaluation visit between treatment with dulaglutide versus placebo. Differences are calculated as the value under treatment with dulaglutide minus placebo, hence, negative differences indicate a reduced water intake under treatment with dulaglutide, while positive values indicate an increased or unaltered water intake under treatment with dulaglutide.

Hypodipsic effect of dulaglutide

After treatment with dulaglutide, acute thirst perception at every time point of the evaluation visit was slightly reduced (see figure 4). Overall thirst perception in the preceding weeks prior to the evaluation visit remained constant with dulaglutide and increased slightly with placebo treatment (see figure 5).

Reported fluid intake decreased in patients receiving dulaglutide during the three weeks of treatment and was significantly lower preceding the evaluation visit (placebo: 4000 [3500, 5000], dulaglutide: 3000 [2500, 3900], on average -1661 ml [-2346, -976] (p-value < 0.001)), figure 6. Less than half of patients reported drinking at night before treatment start.

Self-reported urinary emictions per day before the evaluation visit decreased with dulaglutide as compared to placebo treatment: -1.9 emictions per day [-3.4, -0.5] p = 0.014. During placebo treatment, 16 patients reported nycturia before start of treatment and only 1 patient reported improvement of symptoms. During dulaglutide treatment, 19 patients reported nycturia before treatment start. Of these, 7 patients reported no more nycturia at the evaluation visit. The patient who improved under placebo also improved under dulaglutide (p-value 0.0412).

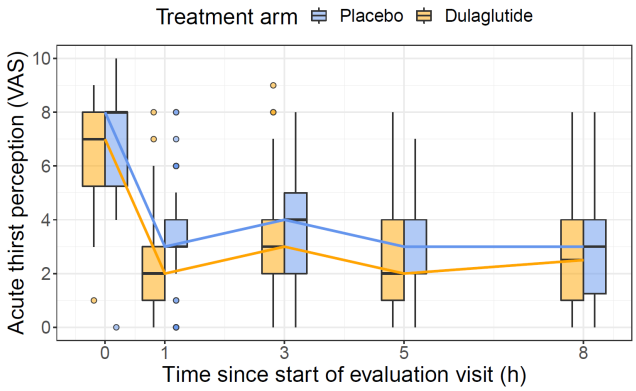

Figure 4: Time course of acute thirst perception (numerous rating scale 0–10) at the evaluation visit for each treatment.

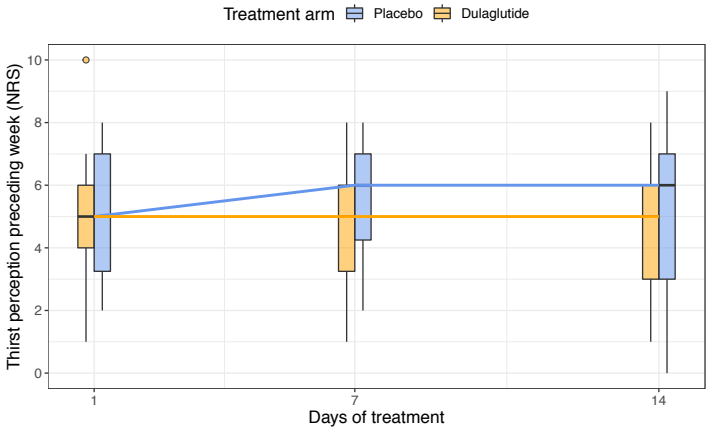

Figure 5: Time course of overall thirst perception during the preceding week for each treatment.

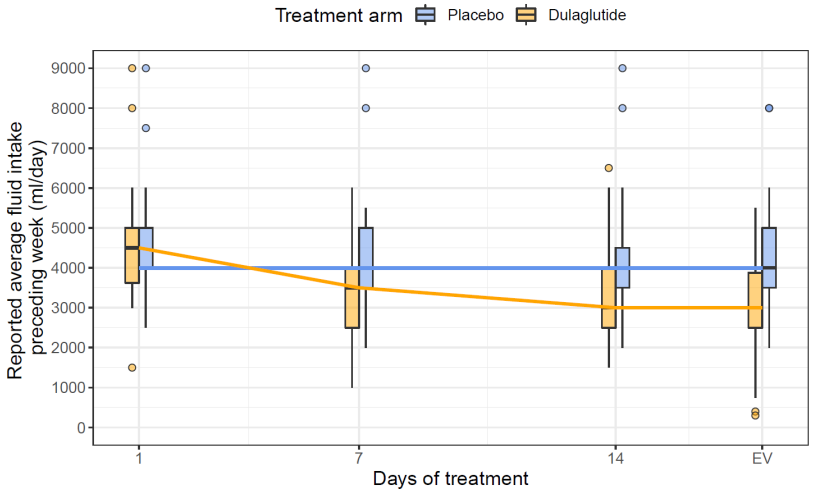

Figure 6: Time course of self-reported average daily fluid intake during the preceding week under treatment with dulaglutide or placebo. Treatment duration was 14 days; the evaluation visit (EV) took place one to six days after the end of treatment (day 15 to 20).

Quality of life

At baseline, patients indicated that their quality of life was reduced by symptoms of polyuria-polydipsia. At the evaluation visit, patients reported an improved quality of life in regard to polyuric-polydipsic symptoms after treatment with dulaglutide as compared to placebo (estimated treatment difference [95%]: -1.6 [-2.9, -0.3], p-value = 0.019).

At the evaluation visit the SF-12 physiological and mental subscores were similar between the two treatment groups at the evaluation visit (p-value = 0.87).

Serum and urinary laboratory parameters

At the beginning of the evaluation visit, patients' serum sodium levels were in the normal range and did not differ between treatment with dulaglutide or placebo (median [IQR] serum sodium levels of 140 mmol/l [138; 141] versus 140 mmol/l [138; 141]). As expected, serum glucose levels were lower on dulaglutide versus placebo treatment (estimated difference -0.63 [-0.86, -0.4] mmol/l, p-value <0.001) but without hypoglycemia.

24-hour urine electrolytes were similar after treatment with dulaglutide as compared to placebo. Particularly, our data provide no evidence that urinary sodium excretion differs between the groups (estimated difference: -8.67 [-19.37, 1.82] mmol/l, p=0.12), see Table 2.

Table 2: Laboratory parameters at the beginning of the evaluation visit

Blood parameters	**Placebo**	**Dulaglutide**
Sodium (mmol/l), median (IQR)	140 (139-142)	140 (139-141)
Osmolality (mosm/kg), median (IQR)	289 (286-292)	286 (284-293)
Creatinine (mmol/l), median (IQR)	70 (62-81)	73 (62-82)
Urea (mmol/l), median (IQR)	4.15 (3.32-5.15)	3.85 (3.12-5.0)
Glucose (mmol/l), median (IQR)	4.8 (4.5-5.2)	4.4 (4.2-4.7)
Urinary parameters	**Placebo**	**Dulaglutide**
Sodium (mmol/l), median (IQR)	38 (26-54)	40 (29-48)
Osmolality (mosm/kg), median (IQR)	217 (154-269)	245 (170-270)
Creatinine (mmol/l), median (IQR)	3.2 (1.9-4.1)	3.7 (2.5-5.0)
Urea (mmol/l), median (IQR)	188 (129-313)	209 (66-282)
Glucose (mmol/l), median (IQR)	0.1 (0-0.1)	0.1 (0-0.1)

Adverse effects

Observed adverse effects were mostly of gastrointestinal nature, e.g. nausea, abdominal pain and diarrhea (Table 3). After treatment with dulaglutide respectively placebo, 11 respectively 6 patients indicated nausea and 3 respectively 2 patients reported abdominal pain during the evaluation visit. Other gastrointestinal symptoms were reported by 2 per each group. Two patients developed mild hyponatremia during both evaluation visits (minimum plasma sodium of patient 1 under dulaglutide was 133 mmol/l, and under placebo 131 mmol/l, minimum plasma sodium of patient 2 under dulaglutide was 133 mmol/l, and under placebo 133 mmol/l).

Table 3: Gastrointestinal symptoms and adverse effects during the evaluation visit

Gastrointestinal symptoms	**Placebo**	**Dulaglutide**
Nausea, n (%)	2 (6)	2 (6)
Abdominal pain, n (%)	1 (3)	2 (6)
Other gastrointestinal symptoms, n (%)	2 (6)	2 (6)
Mild hyponatremia, n (%)	2 (6)	2 (6)

Discussion

Our results indicate that the GLP-1 receptor agonist dulaglutide reduces fluid intake and thirst perception as compared to placebo in patients with primary polydipsia. Consequently, patients receiving dulaglutide were less constrained by drinking and urinary frequency.

Patients with primary polydipsia are characterized by exaggerated thirst sensation and excessive drinking [47]. It may result in water intoxication and life-threatening hyponatremia, highlighting that this condition is not harmless as it is often believed [48,124]. Treatment options have been mainly studied in the psychiatric setting in polydipsic patients with chronic schizophrenia. Besides behavioral therapy [34,35], mainly antipsychotics have been described to be helpful [39,42,119]. However, antipsychotic medications are not a sensible treatment option for otherwise healthy patients, as they are associated with risks of obesity, type 2 diabetes and cardiovascular events [189,190].

In our study median total fluid intake in patients with primary polydipsia was lower on dulaglutide as compared to placebo treatment. Concomitantly, further hypodipsic effects were evident such as reduced self-reported fluid intake, reduced daytime urinary frequency and reduced nycturia. GLP-1 receptor agonists have mainly been studied in food intake, obesity and type 2 diabetes. Findings from rodents and humans have suggested a hypodipsic effect of GLP-1 receptor agonists in an acute setting after single doses of GLP-1 receptor agonists [22,23]. The reduced fluid intake was observed both in the presence and absence of food, indicating a food independent effect of dulaglutide on fluid intake [187]. Our results indicate a prolonged effect of GLP-1 receptor agonists in humans in a controlled setting. In addition, our results show for the first time besides reduced fluid intake effects of GLP-1 on urine output, daytime and nighttime urinary frequency. These results strengthen the observed hypodipsic effect of GLP-1 receptor agonists as an independent effect of food intake.

The most common complication in patients with primary polydipsia is hyponatremia [26,42,48]. It has been described that profound hyponatremia (plasma sodium <125 mmol/l) occurs in patients with primary polydipsia either in the presence of factors impairing renal water excretion, such as medication, acute infection or stress in general, or if free fluid intake exceeds free fluid excretion [27,48,62]. In our cohort, two patients experienced mild hyponatremia in the afternoon in both treatment phases. Even though their fluid intake decreased under dulaglutide as compared to placebo (5400 ml vs 6500 ml and 6700 ml vs 7400 ml), their fluid intake was still very high. One patient received quetiapine, a neuroleptic known to induce hyponatremia, while no clear risk factor for hyponatremia could be identified in the other patient. We speculate that in patients with primary polydipsia, the risk of hyponatremia increases throughout the day with the consistent increase of fluid intake.

The regulation of thirst and drinking is complex and only partly understood (18,19). To coordinate water intake and fluid balance, the brain has to integrate both homeostatic and behavioral signals (20). After salt ingestion an early signal to drink is sent to the brain in order to anticipate hyperosmolality.

Likewise, fluid intake is calibrated to match physiological need and drinking stops before osmolality and blood volume effectively change (21). A role for GLP-1 in this regulatory circuit has been suggested by a recent study in mice (20). The authors found enriched GLP-1 receptor expression in neurons of the lamina terminalis – a key brain structure for sensing and regulating water balance (18, 22). These neurons are believed to be activated by GLP-1 upon water intake and to confer rapid satiety of thirst during fluid ingestion (20). Furthermore, the authors observed a polydipsic overdrinking phenotype after ablation of these GLP-1 receptor expressing, thirst inhibitory neurons. In patients with primary polydipsia, it is speculated that a dysfunction in the brain leads to exaggerated thirst sensation and excessive drinking (23). Additionally, the compulsory fluid intake in primary polydipsia shares similar features with other addictive behaviors such as excessive eating or drug taking (26, 27). Interestingly, growing literature imply that GLP-1 is also involved in reward regulation and the pathophysiology of addiction (26). Indeed, GLP-1 receptors are expressed in brain areas related to reward processing such as hypothalamus, ventral tegmental area and nucleus accumbens (1, 2, 28) supporting this hypothesis. A treatment with GLP-1 receptor agonists holds, therefore, the potential to address addictive components of primary polydipsia while also modulating homeostatic and behavioral factors of thirst regulation.

The main limitation of this study is the short observation period of 8 hours and the artificial setting used to assess the primary endpoint, water intake. Nevertheless, the reduced fluid intake in patients receiving dulaglutide is in line with findings from the literature, where fluid intake was reported alongside food intake. Self-reported fluid intake indicated a stronger effect of hypodipsic properties in patients receiving GLP-1 receptor agonists. The appetite and thirst satiating effects of GLP-1 receptor agonists may be linked to their well-known impact on nausea or taste aversion [191]. In our study, reported nausea and side effects during the evaluation visit were similar between the two groups and the model adjusting for side effects confirmed reduced fluid intake in patients receiving dulaglutide. This indicates that the observed hypodipsic effects of dulaglutide were independent of gastrointestinal side effects. Last but not least, we used dulaglutide as study drug and are not able to transfer these results to other GLP-1 receptor agonists. Dulaglutide is a large molecule (>50-60 kilo Dalton) and its size may hamper the access to the central nervous system [192]. The effect on fluid intake could be more pronounced with smaller GLP-1 receptor agonist molecules of enhanced blood brain barrier permeability and central activity (e.g. liraglutide, semaglutide or lixisenatide) [193].

In summary, our data show that a 3-week treatment with the GLP-1 receptor agonist dulaglutide reduces fluid intake and polydipsic symptoms in patients with primary polydipsia. Further large scale and longer intervention studies also with other GLP-1 receptor agonists should be conducted to confirm our results. This study is a first approach to provide a new treatment option for patients with primary polydipsia, where currently no effective medical treatment options exist.

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Disclosure summary

The authors have nothing to disclose.

Other published original articles (first author)

Effects of alcohol consumption on copeptin levels and sodium-water homeostasis

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* C.O.S. and J.R. contributed equally to this work.

Alcohol consumption influences the sodium-water homeostasis. However, the effect of alcohol on vasopressin levels is controversial. The aim of this study was to evaluate physiological changes of alcohol consumption on the stable vasopressin surrogate marker copeptin. In addition, we aimed at investigating the effect of additional sodium and/or water consumption on plasma sodium, osmolality and copeptin levels. Ten healthy men underwent four interventions in random order: a) beer consumption only, b) beer consumption with additional water or c) stock, d) water consumption only. Fluid consumption was equal between interventions and calculated to reach a blood alcohol concentration of 0.8‰ in the beer interventions. Blood and urinary samples were taken at six timepoints over the observation period of 720 minutes. The primary endpoint was the mean difference in copeptin levels 90 minutes after the start of fluid consumption, which showed no in-between groups differences (p=0.4). However, a higher total urinary volume excretion in all alcohol compared to water interventions was observed (p=0.01). Furthermore, plasma copeptin, sodium and urinary osmolality levels increased significantly at the end of the observation period in all alcohol compared to water only interventions (p=0.02). In conclusion, initial copeptin suppression does not differ between alcohol or water interventions but seems to be prolonged in the alcohol interventions. This leads to increased volume loss followed by a counter regulation with increased copeptin levels and water retention after 720 minutes in the alcohol compared to interventions. Additional sodium and/or water consumption with alcohol did not change the observed alcohol-induced effects.

Mild to moderate hyponatremia at discharge is associated with increased risk of recurrence in patients with community-acquired pneumonia

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* L.P, C.O.S. and C.A.B. contributed equally contributing to this manuscript

Background: Hyponatremia is the most common electrolyte disorder in hospitalized patients with pneumonia. Different studies have shown an association of hyponatremia on admission and worse patient's outcome. Yet, the impact of hyponatremia at discharge or of hyponatremia correction on patient's prognosis is unknown.

Methods: This is a preplanned secondary data analysis from a double-blind, randomized, placebo-controlled trial of hospitalized patients with community-acquired pneumonia and prednisone treatment. The primary outcome was the impact of hyponatremia on admission and at discharge on patient relevant outcomes (i.e. mortality, rehospitalization and recurrence rate) within 180 days.

Results: Of the 708 included patients, 185 (26.1%) were hyponatremic on admission. Of these, 28 (15.1%) were still hyponatremic at discharge. 34 (4.8%) patients developed hyponatremia during hospitalization despite being normonatremic on admission. Patients with hyponatremia at discharge had a higher rate of pneumonia recurrence as compared to normonatremic patients (OR 2.68; 95%-CI 1.09–6.95; p = 0.037). Among patients with hyponatremia at discharge, patients who were already hyponatremic on admission showed the strongest association with increased recurrence rate (OR 4.01; 95%-CI 1.08–12.64; p = 0.022). In contrast, recurrence rate was not affected in patients who were hyponatremic on admission but had normalized serum sodium levels at discharge (p = 0.73).

Conclusion: Mild to moderate hyponatremia at discharge is associated with an increased risk of recurrence in hospitalized patients with pneumonia. This association is particularly strong for patients who are hyponatremic both on admission and at discharge, emphasizing the importance of hyponatremia correction during hospitalization.

Markers of systemic inflammation in response to osmotic stimulus in healthy volunteers

Clara Odilia Sailer, Sophia Julia Wiedemann, Konrad Strauss, Ingeborg Schnyder, Wiebke Kristin Fenske and Mirjam Christ-Crain

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Osmotic stimulus or stress results in vasopressin release. Animal and human in vitro studies have shown that inflammatory parameters, such as interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α), increase in parallel in the central nervous system and bronchial, corneal or intestinal epithelial cell lines in response to osmotic stimulus. Whether osmotic stimulus directly causes a systemic inflammatory response in humans is unknown. We therefore investigated the influence of osmotic stimulus on circulatory markers of systemic inflammation in healthy volunteers. In this prospective cohort study, 44 healthy volunteers underwent a standardized test protocol with an osmotic stimulus leading into the hyperosmotic/hypernatremic range (serum sodium ≥150 mmol/L) by hypertonic saline infusion. Copeptin – a marker indicating vasopressin activity – serum sodium and osmolality, plasma IL-8 and TNF-α were measured at baseline and directly after osmotic stimulus. Median (range) serum sodium increased from 141 mmol/L (136, 147) to 151 mmol/L (145, 154) ($P < 0.01$), serum osmolality increased from 295 mmol/L (281, 306) to 315 mmol/L (304, 325) ($P < 0.01$). Median (range) copeptin increased from 4.3 pg/L (1.1, 21.4) to 28.8 pg/L (19.9, 43.4) ($P < 0.01$). Median (range) IL-8 levels showed a trend to decrease from 0.79 pg/mL (0.37, 1.6) to 0.7 pg/mL (0.4, 1.9) ($P < 0.09$) and TNF-α levels decreased from 0.53 pg/mL (0.11, 1.1) to 0.45 pg/mL (0.12, 0.97) ($P < 0.036$). Contrary to data obtained in vitro, circulating proinflammatory cytokines tend to or decrease in human plasma after osmotic stimulus. In this study, osmotic stimulus does not increase circulating markers of systemic inflammation.

The challenges of sodium measurements: indirect versus direct ion-selective method

Julie Refardt*, Clara Odilia Sailer*, Irina Chifu, Bettina Winzeler, Ingeborg Schnyder, Martin Fassnacht, Wiebke Fenske and Mirjam Christ-Crain on behalf of the CODDI-Investigators

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* J.R. and C.O.S. contributed equally contributing to this manuscript

Background: Diagnosis and treatment of dysnatremia is challenging and further complicated by the pitfalls of different sodium measurement methods. Routinely used sodium measurements are the indirect (plasma/serum) and direct (whole blood) ion-selective electrode (ISE) method, showing discrepant results especially in the setting of acute illness. Few clinicians are aware of the differences between the methods in clinically stable patients or healthy volunteers.

Methods: Data of 140 patients and 91 healthy volunteers undergoing osmotic stimulation with hypertonic saline infusion were analyzed. Sodium levels were measured simultaneously by indirect and direct ISE method before and at different time points during osmotic stimulation up to a sodium threshold of ≥150 mmol/L. The primary outcome was the difference in sodium levels between the indirect and direct ISE method.

Results: 878 sodium measurements were analyzed. Mean (s.d.) sodium levels ranged from 141 mmol/L (2.9) to 151 mmol/L (2.1) by the indirect ISE compared to 140 mmol/L (3) to 149 mmol/L (2.8) by the direct ISE method. The interclass correlation coefficient between the two methods was 0.844 (95% CI: 0.823–0.863). On average, measurements by the indirect ISE were 1.9 mmol/L (95% CI limits: −3.2 to 6.9) higher than those by the direct ISE method ($P < 0.001$). The tendency of the indirect ISE method resulting in higher levels increased with increasing sodium levels.

Conclusion: Intra-individual sodium levels differ significantly between the indirect and direct ISE method also in the absence of acute illness. It is therefore crucial to adhere to the same method in critical situations to avoid false decisions due to measurement differences.

Published original articles (co-author)

A Randomized Trial of Empagliflozin to Increase Plasma Sodium Levels in Patients with the Syndrome of Inappropriate Antidiuresis

Julie Refardt, Cornelia Imber, Clara O. Sailer, Nica Jeanloz, Laura Potasso, Alexander Kutz, Andrea Widmer, Sandrine Urwyler, Fahim Ebrahimi, Deborah R. Vogt, Bettina Winzeler, Mirjam Christ-Crain

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Background: The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the predominant cause of hyponatremia but its treatment options are unsatisfying. The SGLT2-inhibitor empagliflozin promotes osmotic diuresis via urinary glucose excretion and could therefore be a novel treatment option for SIADH.

Methods: From 09/2016 until 12/2018 we recruited 88 hospitalized patients with hyponatremia <130mmol/l due to SIADH in the University Hospital Basel. Patients were randomly assigned to either treatment with empagliflozin 25mg/day or placebo for four days in addition to standard fluid restriction of <1000ml/24h. The primary endpoint was the absolute change in plasma sodium concentration after four days of treatment.

Results: 87 patients completed the trial of whom 43 (49%) received treatment with empagliflozin and 44 (51%) placebo. Severity of the SIADH was similar, with a median plasma sodium concentration of 125.5 mmol/l (IQR:122-127) and 126 mmol/l (IQR:123-127) in the empagliflozin and placebo group respectively. Treatment with empagliflozin resulted in a significantly higher increase of median plasma sodium concentration of 10mmol/l (IQR:5–12) compared to placebo with 7mmol/l (IQR:3–11), p=0.038. Severity of hyponatremia (<125 mmol/l) and baseline osmolality levels were predisposing factors for treatment response with empagliflozin. Treatment was tolerated well, no events of hypoglycemia or hypotension occurred. One severe adverse event involving transient reduction in kidney function was related to empagliflozin.

Conclusion: Empagliflozin in addition to fluid restriction leads to a higher increase in plasma sodium levels compared to placebo in patients with SIADH and is therefore a promising new treatment option.

Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study

Bettina Winzeler, Nicole Cesana-Nigro, Julie Refardt, Deborah R Vogt, Cornelia Imber, Benedict Morin, Milica Popovic, Michelle Steinmetz, Clara O Sailer, Gabor Szinnai, Irina Chifu, Martin Fassnacht, Mirjam Christ-Crain

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Background Differential diagnosis of diabetes insipidus is challenging. The most reliable approach is hypertonic saline-stimulated copeptin measurements. However, this test is based on the induction of hypernatraemia and requires close monitoring of plasma sodium concentrations. Arginine-stimulated copeptin measurements might provide an alternative, simple, and safe test.

Methods In this prospective diagnostic study, we recruited a development cohort from University Hospital Basel, Basel, Switzerland, and a validation cohort from five centres in Basel, Aarau, Luzern, Bern, and St Gallen, Switzerland, and the University Hospital Würzburg, Würzburg, Germany. For both cohorts, patients were eligible for inclusion if they were aged 18 years or older, were newly referred with polyuria (>50 mL/kg bodyweight per day) or had a known diagnosis of central diabetes insipidus or primary polydipsia. We also recruited a comparator cohort of healthy controls in parallel to each cohort, comprising adults (aged 18 years and older, with normal drinking habits, and no history of polyuria) and children who underwent arginine stimulation to diagnose growth hormone deficiency (children were only included in the comparator cohort to the development cohort as proof of concept). Patients and healthy controls underwent arginine stimulation with measurement of plasma copeptin at baseline and 30, 45, 60, 90, and 120 min. The primary objective in the development cohort was to determine the diagnostic accuracy of plasma copeptin concentrations to discriminate between diabetes insipidus and primary polydipsia, and in the validation cohort was to confirm those results. Adverse effects of the test were monitored in all participants, with tolerability of the test rated using a visual analogue scale (VAS) that ranged from no (0) to maximum (10) discomfort. This trial is registered with ClinicalTrials.gov, number NCT00757276.

Findings Between May 24, 2013, and Jan 11, 2017, 52 patients were enrolled in the development cohort (12 [23%] with complete diabetes insipidus, nine [17%] with partial diabetes insipidus, and 31 [60%] with primary polydipsia) alongside 20 healthy adults and 42 child controls. Between Oct 24, 2017, and June 27, 2018, 46 patients were enrolled in the validation cohort (12 [26%] with complete diabetes insipidus, seven [15%] with partial diabetes insipidus, and 27 [59%] with primary polydipsia) alongside 30 healthy adult controls (two patients in this cohort were excluded from the main analysis

because of early vomiting during the test). In the pooled patient and control datasets, median arginine-stimulated copeptin concentrations increased in healthy adult controls (from 5·2 pM [IQR 3·3–10·9] to a maximum of 9·8 pM [6·4–19·6]) and in participants with primary polydipsia (from 3·6 pM [IQR 2·4–5·7] to a maximum of 7·9 pM [5·1–11·8]), but only minimally in those with diabetes insipidus (2·1 pM [IQR 1·9–2·7] to a maximum of 2·5 pM [1·9–3·1]). In the development cohort, a cutoff of 3·5 pM at 60 min provided the highest diagnostic accuracy of 94% (95% CI 84–98). The accuracy of this cutoff in the validation cohort was 86% (95% CI 73–94). By pooling the data from both cohorts, an optimal accuracy of 93% (95% CI 86–97) was reached at a cutoff of 3·8 pM copeptin at 60 min (sensitivity 93%, 95% CI 86–98; specificity 92%, 95% CI 84–100). The test was safe and well tolerated, with median VAS scores of 3·5 (IQR 2–4) in patients with diabetes insipidus, 3 (2–4) in those with primary polydipsia, 1 (1–3) in healthy adults, and 1 (0–5) in healthy children in the pooled participant dataset.

Interpretation Arginine-stimulated copeptin measurements are an innovative test for diabetes insipidus with high diagnostic accuracy, and could be a simplified, novel, and safe diagnostic approach to diabetes insipidus in clinical practice.

Effects of Glucagon-Like Peptide-1 Receptor Agonists on Hypothalamic-Pituitary-Adrenal Axis in Healthy Volunteers

Bettina Winzeler, Ismael da Conceiçao, Julie Refardt, Clara O. Sailer, Gilles Dutilh, and Mirjam Christ-Crain

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Context: Recent findings from animal and human studies indicate that glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) modulate stress response by activating the hypothalamic-pituitary- adrenal (HPA) axis, which may have relevant clinical implications.

Objective: To investigate the influence of GLP-1 RA treatment on HPA axis activity compared with placebo in healthy volunteers.

Design: Double-blind, randomized, crossover study.

Setting: University Hospital Basel, Switzerland.

Participants: Twenty healthy volunteers.

Intervention: Dulaglutide (Trulicity®) 1.5 mg and placebo (0.9% sodium chloride) were given subcutaneously once weekly for 3 weeks.

Main Outcome Measures: Twenty-four-hour urinary free cortisol, circadian rhythm of serum and salivary cortisol, cortisol after 1 mg dexamethasone suppression test, and cortisol levels before and after stimulation with ACTH.

Results: Urinary free cortisol levels were similar under dulaglutide [median (interquartile range) 240 nmol/L (164, 324)] vs placebo [188 nmol/L (133, 338), P = 0.131]. The circadian rhythm of serum and salivary cortisol were comparable in both groups as were cortisol levels after dexamethasone [dulaglutide 28 nmol/L (22, 47.5) vs placebo 26.5 nmol/L (15.8, 45.5), P = 0.4]. Serum cortisol levels in dulaglutide and placebo treated participants were 522 nmol (388, 710) and 530 nmol/L (394, 747), before (P = 0.6), and 658 nmol/L (604, 810) and 636 nmol/L (512, 910) after ACTH stimulation (P = 0.87).

Conclusion: Our results suggest that there is no activation of the HPA axis by long-term GLP-1 RA exposure, particularly dulaglutide, at the medically approved dosage of 1.5 mg once weekly.

FGF-21 levels in polyuria-polydipsia syndrome

Julie Refardt, Clara Odilia Sailer, Bettina Winzeler, Matthias Johannes Betz, Irina Chifu, Ingeborg Schnyder, Martin Fassnacht, Wiebke Fenske and Mirjam Christ-Crain for the CODDI-Investigators

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The pathomechanism of primary polydipsia is poorly understood. Recent animal data reported a connection between fibroblast growth factor 21 (FGF-21) and elevated fluid intake independently of hormonal control by the hormone arginine-vasopressin (AVP) and osmotic stimulation. We therefore compared circulating FGF-21 levels in patients with primary polydipsia to patients with AVP deficiency (central diabetes insipidus) and healthy volunteers. In this prospective cohort study, we analyzed FGF-21 levels of 20 patients with primary polydipsia, 20 patients with central diabetes insipidus and 20 healthy volunteers before and after stimulation with hypertonic saline infusion targeting a plasma sodium level ≥150 mmol/L. The primary outcome was the difference in FGF-21 levels between the three groups. Baseline characteristics were similar between the groups except for patients with central diabetes insipidus being heavier. There was no difference in baseline FGF-21 levels between patients with primary polydipsia and healthy volunteers (122 pg/mL (52,277) vs 193 pg/mL (48,301), but higher levels in patients with central diabetes insipidus were observed (306 pg/mL (114,484); P=0.037). However, this was not confirmed in a multivariate linear regression analysis after adjusting for age, sex, BMI and smoking status. Osmotic stimulation did not affect FGF-21 levels in either group (difference to baseline: primary polydipsia −23 pg/mL (−43, 22); central diabetes insipidus 17pg/mL (−76, 88); healthy volunteers −6pg/mL (−68, 22); P=0.45). To conclude, FGF-21 levels are not increased in patients with primary polydipsia as compared to central diabetes insipidus or healthy volunteers. FGF-21 therefore does not seem to be causal of elevated fluid intake in these patients.

Discussion and outlook

The main findings of my MD-PhD thesis are the following: First, one third of patients with primary polydipsia hospitalized with profound hyponatremia has no psychiatric comorbidity. Second, every patient with primary polydipsia has a contributing factor, i.e. medication, acute infection, or nausea, leading to an impaired renal water excretion, resulting in hyponatremia. Third, especially profound hyponatremia is more common during summer months regardless of the underlying cause and patients with primary polydipsia tend to experience hyponatremia more commonly with increased outdoor temperature. Fourth, arginine infusion is a non-osmotic stimulus of the posterior pituitary and arginine stimulated copeptin levels can differentiate between patients with primary polydipsia and diabetes insipidus with a high diagnostic accuracy. Lastly, GLP-1 receptor agonists reduce fluid intake in patients with primary polydipsia. Additionally,
The one-year follow-up of the study regarding prevalence, characteristics, and outcome of patient with primary polydipsia and acute psychosis as well as the data analysis of the neuroimaging study are still ongoing.

According to the analysis of a large prospective study in patients with profound hyponatremia presenting at the emergency department, 8% of patients were identified to suffer from primary polydipsia [127]. Our results confirm that a high percentage of patients with primary polydipsia have a psychiatric comorbidity, mainly addictive disorder, depression, and personality disorders [48]. The prevalence of a schizophrenia spectrum disorder was surprisingly low, and no patient suffered from an acute psychotic episode, possibly due to the fact that these patients are usually treated in the psychiatric department despite profound hyponatremia. Importantly, however, one third of patients had no psychiatric comorbidity. This underlines that primary polydipsia is a phenomenon which is increasingly present outside the psychiatric setting and may result in hyponatremia. We identified a factor contributing to the development of hyponatremia in every patient. While acute fluid intake of large amounts was identified as primary cause of hyponatremia in some patients, a factor impairing renal water excretion was present in every patient. Impaired renal water excretion be caused by reduced solute intake leading to a reduced capacity of the kidneys to excrete water, as it has been shown that the kidneys require a minimum amount of solutes to excrete fluids [27,62]. We hypothesize that in our cohort, especially in patients with beer potomania and anorexia nervosa, hyponatremia was at least partly caused by reduced solute intake due to food deprivation. Another factor limiting renal excretion capacity is a concomitant stimulus of the water and sodium balance regulating hormone vasopressin. Several trigger factors, such as antidepressant or antidiuretic drugs, pain, nausea, acute infections, especially pneumonia, and urogenital tract infections, and stress in general, can lead to an unspecific increase of vasopressin and alter the sodium-water balance. It is therefore

important to control sodium levels regularly in patients with known polydipsia, especially in the presence of any of the described contributing factors. Lastly, we found in our cohort that patients with primary polydipsia had an overall poor outcome with an increased rehyponatremia, rehospitalization, and even mortality rate. These data are important to bear in mind in treating hospitalized patients with primary polydipsia and measure should be implemented to prevent hyponatremia.

The general advice is to increase fluid intake when outdoor temperature rises to compensate for the fluid loss from sweating [194]. Based on observations from clinical routine we speculated that hyponatremia prevalence increases during summer months. Our main finding was that especially profound hyponatremia prevalence increases during summer months and correlates with outdoor temperature [49,50]. There was furthermore a trend towards a higher hyponatremia rate due to primary polydipsia during increased outdoor temperatures. In the general population, we showed that the prevalence of hyponatremia, and especially during summer months, is elevated for female and elderly patients. We speculate that the combination of low fluid and solute intake, or consumption of primarily hypotonic fluids, together with the contributing factors discussed above increases the risk of hyponatremia. Our data raises the question whether the general recommendation of increased fluid intake, especially in summer months, may increase the risk for hyponatremia and associated poor outcome. The general recommendation from health authorities is to drink 1,500-2,000 ml of fluid per day. In the ley press, increased water intake is often called detoxifying, leading to a cleaner skin, better concentration, and improved digestion and the advice is “to drink plenty of water”. According to our results however, unspecific recommendation of increased fluid intake could lead to the intake of excessive amounts of fluid and with this an increased risk of hyponatremia, especially in patients with predisposing factors for an altered renal water excretion. It is therefore important to inform people that the daily fluid requirement is individual and that too much water intake is possible and associated with complications. Maybe we should consider also for water intake the quote of Paracelsus: *All things are poison and nothing (is) without poison; only the dose makes that a thing is no poison*.

Current treatment options for patients with primary polydipsia are scarce. As primary polydipsia has mainly been described in the psychiatric setting, it is not surprising that most investigated treatment options are antipsychotics. Our results and the rising number of case reports indicate that primary polydipsia is also common in patients with depression and otherwise healthy people. Treating these patients with antipsychotics, medications that have nonetheless unfavorable side effects, such as weight gain, type 2 diabetes, and cardiovascular complications, is irresponsible. Behavioral therapy, even though the currently most efficient treatment option for patients with primary polydipsia, is time intensive and requires manpower, which limits its feasibility in the outpatient setting [34–37]. The gut

hormone glucagon-like peptide-1 (GLP-1) is has been shown to regulate appetite and energy balance and GLP-1 receptor agonists are successfully used to treat patients with type 2 diabetes mellitus and obesity [168–171]. The satiating properties of GLP-1 and its receptor agonists make these medications an interesting therapeutic option for regulating drinking and water-sodium homeostasis [172,173]. In our study, fluid intake following a three-week treatment period with the GLP-1 receptor agonist dulaglutide showed a significant and clinically relevant fluid reduction of 15% in patients with primary polydipsia as compared to placebo. In addition, patients reported reduced fluid intake, reduced daytime urinary frequency and lower restriction by polyuric-polydipsic behavior.

The mechanism of action of GLP-1 and its receptor agonists regulating food and fluid intake is not entirely understood. Regarding food intake, it has been shown that GLP-1 slows gastric emptying and has a glucose dependent insulinotropic effect on the pancreatic beta cells [179,195]. It is further speculated, that GLP-1 acts centrally on reward centers, such as the hypothalamus, the anterior cingulate cortex, the orbitofrontal cortex, the insula and putamen, and reduces brain activity in response to highly desirable food cues [196,197]. Similar brain areas are also involved in thirst, drinking and overdrinking [11,12]. No study has yet investigated brain activity when exposed to drinking stimuli in patients with primary polydipsia. We can only speculate, but it seems plausible that primary polydipsia could be caused by a dysfunction in these centers, making GLP-1 receptor agonists a promising treatment option for those patients. Our ongoing analysis could clarify some of the mechanisms how GLP-1 receptor agonists act on the brain.

In conclusion, the general recommendation of increased fluid intake during summer months and hot weather should be specified and individualized to prevent overdrinking and hyponatremia. Patients with primary polydipsia should be carefully monitored and factors altering the renal water excretion kept to a minimum to prevent the development of hyponatremia. GLP-1 receptor agonists might be a new treatment option for patients with primary polydipsia.

Direction for future research

Even though many of the questions regarding primary polydipsia, its complications, and potential treatment options have been addressed by this MD-PhD, some open questions remain.

The ongoing trial in psychiatric patients will provide evidence of the current prevalence of primary polydipsia in patients with acute psychosis. However, ideal amount of drinking and the prevalence of primary polydipsia in the general population remains unclear. Nationwide data on fluid intake, urinary excretion, and electrolytes could be used to assess the current daily fluid intake, providing evidence towards the ideal amount of daily fluid intake and the prevalence of primary polydipsia in the general population.

The ongoing analysis of neuroimaging studies in patients with primary polydipsia in comparison to healthy controls will clarify involved brain areas in the polydiptic patients and contribute to the pathophysiological understanding of the disorder. Furthermore, our data will provide evidence towards the role of GLP-1 receptor agonists in thirst and drinking regulation. However, whether other central hormones or neurotransmitters are involved in the development of hyponatremia has to be discussed and further researched.

The study investigating the GLP-1 receptor agonist dulaglutide to reduce fluid intake is the first study of this medication class as treatment option for patients with primary polydipsia. Large-scale studies also with other GLP-1 receptor agonists are necessary to confirm these data to ultimately accept these medications as treatment option for patients with primary polydipsia in clinical routine.

Conclusion and closing remark

This MD-PhD thesis focuses on patients with primary polydipsia in the medical and psychiatric setting, a common but neglected disorder. The results of the published and further planned papers and studies contribute significantly to the pathophysiological understanding of the disorder, its main complication hyponatremia, and potential treatment options. The studies performed as part of my MD-PhD have clarified some of the unanswered questions in the field of primary polydipsia. However, uncertainty about this disorder remains: a.) the prevalence of primary polydipsia in the general population, b.) the role of GLP-1 and other hormones in the development of primary polydipsia, and c.) the most beneficial treatment option. Based on my publications, future studies can be planned to answer these research questions.

In conclusion, I am confident that not only have I learned how to perform clinical research from the planning of a trial, to the conduction, data analysis, and manuscript writing, but also have I contributed significantly to the knowledge about patients with primary polydipsia. I am very excited and motivated to continue clinical research in this field and improve my personal skills as well as the general knowledge about patients with primary polydipsia.

“And those who were seen dancing were thought to be insane
by those who could not hear the music.”

“Die Tanzenden wurden für verrückt gehalten
von denjenigen, die die Musik nicht hören konnten. ”

— Friedrich Nietzsche

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Curriculum vitae

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Education and Specializations

Since 09/2016	MD-PhD, Endocrinology Clinical Research, Basel University (CH)
	Title: *Primary polydipsia in the medical and psychiatric patient*
	Supervisor: Prof Mirjam Christ-Crain, Prof Stefan Borgwardt
02/2017 – 05/2019	Master's Program in Clinical Research, Dresden International University (D) and Harvard T.H. Chan School of Public Health (USA)
	Supervisor: Prof Felipe Fregni (USA), Dr Timo Siepmann (D)
29/09/2017	Doctor of Medicine, Basel University (CH)
	Supervisor: Prof Mirjam Christ-Crain
04/10/2016	Swiss Federal Medical Examination (CH)
09/2013 – 09/2016	Master of Human Medicine**,** Basel University (CH)
	Supervisor: Prof Mirjam Christ-Crain
09/2010 - 07/2013	Bachelor of Human Medicine, Fribourg University (CH)
09/2009 - 08/2010	Bachelor in Biomedical Sciences, Fribourg University (CH)

Employment history

Since 09/2016	MD-PhD, Endocrinology Clinical Research, Basel University (CH)
	Supervisor: Prof Mirjam Christ-Crain, Prof Stefan Borgwardt
	Funding: Goldschmidt-Jacobson-Stiftung 53'000 CHF,
	University Hospital Basel Pool MD-PhD 85'000 CHF,
	"Young talents in clinical research" Beginner Grant, Bangerter Foundation and Swiss Academy of Medical Science 75'000 CHF
09/2017 - 01/2020	Clinical consultant Endocrinology (20%), University Hospital Basel (CH)
	Advisor: Prof Marc Donath
04/2015 - 02/2016	Clinical Clerkships: Endocrinology, Department of Endocrinology, Diabetology & Metabolism, Basel (CH); Internal Medicine, Swiss Paraplegic Centre, Nottwil (CH); Surgery, Melbourne Royal Hospital, Melbourne (AUS); Geriatrics, Geriatric Hospital St. Gallen (CH); Pediatrics, Pediatric Hospital Basel (CH)
08/2014	Clinical Internship, Neurology, Quebec City (CAN)
09/2012 - 06/2013	Tutorial in anatomy, Fribourg University (CH)

09/2007 - 06/2008	Nursing Internship: Cardiology, Hirslandenklinik Aarau; Internal Medicine and Rehabilitation, Swiss Paraplegic Centre Nottwil; Psychosomatics, Klinik Schützen, Rheinfelden (CH)

Institutional responsibilities

04/2017 - 01/2020	Representative of Clinical PhD students in the steering committee of the PhD Program Health Science, Basel University (CH)
08/2017 - 05/2019	Organizer of the monthly "Science Club Method" of the PhD Program Health Science, Basel University (CH)
10/2013 - 09/2016	Faculty representative of medical students, Basel University (CH)
09/2011 - 09/2013	Active member of the medical students' council, Fribourg University (CH)

Approved research projects

11/2018	Main applicant: "The influence of water and salt intake on copeptin levels during moderate alcohol consumption" (NCT03883503)
12/2017	Co-applicant: "Effects of GLP-1 Analogues on Fluid Intake in Patients With Primary Polydipsia (The GOLD-Study)" sub-study investigating fMRI changes (imagine-GOLD) (NCT02770885)
03/2017	Main applicant: "Copeptin in Outcome Prediction of an Acute Psychotic Episode" (NCT03235908)

Supervision of students/junior researchers

Since 01/2019	Master student: Sarah Bissig

Teaching activities

11/2019	Introduction to endocrinology, Health Master, Lucerne University (CH)
02/2018 - 11/2018	Teaching Assistant Principles and Practice of Clinical Research, Harvard T.H. Chan School of Public Health, Program Director Prof Felipe Fregni, Associate Professor (USA)
02/2018 - 05/2018	Courses for functional insulin therapy for patients with type 1 diabetes, Department of Endocrinology, University Hospital Basel (CH)
02/2013 - 10/2013	Main organizer of three "Training New Trainer" workshops of the International Federation of Medical Students Organization in Berne (CH), Santiago (CHL), Khartoum (SDN)

Membership in panels, boards, etc., and individual scientific reviewing activities

Since 10/2018	Vice-president of the Swiss MD-PhD Association (CH)
09/2011 - 09/2013	Vice president for Internal affairs of the Swiss Medical Students' Association (CH)
2019	Review for the International Journal of Basic and Clinical Endocrinology
2018	Review for American Association of Clinical Endocrinologists
2017	Review for Clinical Endocrinology and Swiss Medical Weekly

Active membership in scientific societies, fellowship in renowned academies

Since 2018	Swiss Medical Association (FMH)
Since 2017	American Endocrine Society (ENDO)
Since 2016	Swiss Society of Endocrinology & Diabetology (SGED)
Since 2016	European Endocrine Society (ESE)
Since 2012	Swiss Association of Residence and Consultants (VSAO)

Organization of conferences

02/2017 - 10/2017	Member of organizing committee of the Swiss MD-PhD conference 2017, Basel (CH)
2010 - 2013	Part of organizing team of 8 Swiss medical students' convention

Prizes, awards and fellowship

01/2020	2nd price best oral presentation "Clinical Research Day" Basel (CH) 1'000 CHF
12/2019	"Early Career Forum and Travel Award", "Outstanding Abstract Award", complimentary registration to ENDO 2020, San Francisco, California (USA) $1'644
11/2019	"Young talents in clinical research" Project Grant, Bangerter Foundation and Swiss Academy of Medical Science (CH) 80'000 CHF
12/2018	"Young talents in clinical research" Beginner Grant, Bangerter Foundation and Swiss Academy of Medical Science (CH) 75'000 CHF
11/2018	"Outstanding Teaching Assistant Award" Principles and Practice of Clinical Research, Harvard T.H. Chan School of Public Health (USA)
05/2018	"Stipend Award for research project" PhD Program Health Sciences, Basel University (CH) 15'000CHF
02/2018 – 11/2018	"antelope@university" Career Program for women, Basel University (CH) 8'000 CHF
11/2017	"Clinical Research Scholar Award" Principles and Practice of Clinical Research, Harvard T.H. Chan School of Public Health (USA)
08/2016	"Doctoral scholarship grant" Margot and Erich Goldschmidt & Peter René Jacobson Foundation, Basel (CH) 53'000 CHF
03/2015	"Karger-Award of Basler Medical Students Science Congress", Basel University (CH)
11/2014	"You Rock swimsa Award" for achievements within the Swiss Medical Student's Association (CH)

Personal skills

Digital competences:	Advanced programming skills in the "R"-language and Microsoft Office and FSL (functional magnet resonance imaging program)
Language:	German (native), English (C1), French (C1)

Career breaks

None