Cost Effectiveness and Resource Allocation

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Cost of illness of hyponatremia in the United States

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Published: 31 May 2006

Cost Effectiveness and Resource Allocation 2006, **4**:10 doi:10.1186/1478-7547-4-10

Received: 27 May 2005
Accepted: 31 May 2006

This article is available from: http://www.resource-allocation.com/content/4/1/10

Abstract

Background: Hyponatremia is a disorder of fluid and electrolyte balance characterized by a relative excess of body water relative to body sodium content. It is the most common electrolyte disorder encountered in clinical medicine and is associated with negative outcomes in many chronic diseases. However, there is limited information in the literature about health care resource use and costs attributable to the effects of the condition. The purpose of this analysis was to estimate the annual cost of illness of hyponatremia in the United States.

Methods: The study utilized a prevalence-based cost of illness framework that incorporated data from publicly available databases, published literature and a consensus panel of expert physicians. Panel members provided information on: classification of hyponatremia patients, treatment settings for hyponatremia (i.e., hospital, emergency room, doctor's office), and health care resource use associated with the diagnosis and treatment of hyponatremia. Low and high prevalence scenarios were estimated and utilized in a spreadsheet-based cost of illness model. Costs were assigned to units of resources and summarized across treatment settings.

Results: The prevalence estimate for hyponatremia ranged from 3.2 million to 6.1 million persons in the U.S. on an annual basis. Approximately 1% of patients were classified as having acute and symptomatic hyponatremia, 4% acute and asymptomatic, 15%–20% chronic and symptomatic, and 75–80% chronic and asymptomatic. Of patients treated for hyponatremia, 55%–63% are initially treated as inpatients, 25% are initially treated in the emergency room, and 13%–20% are treated solely in the office setting. The direct costs of treating hyponatremia in the U.S. on an annual basis were estimated to range between $1.6 billion and $3.6 billion.

Conclusion: Treatment of hyponatremia represents a significant healthcare burden in the U.S. Newer therapies that may reduce the burden of hyponatremia in the inpatient setting could minimize the costs associated with this condition.

Background

Hyponatremia, defined as a serum sodium concentration ($[Na^+]$) less than 135 mEq/L [1], represents a relative excess of body water relative to body sodium content. Clinical symptoms are largely related to dysfunction of the central nervous system, and are more evident when the decrease in the serum sodium concentration is large or fast [2]. Although most hyponatremic patients may

appear to be asymptomatic, severe symptomatic hyponatremia is a medical emergency that calls for immediate treatment. Complications of severe and rapidly developing hyponatremia can include seizures, coma, brain-stem herniation, respiratory arrest, permanent brain damage, and death [3].

Hyponatremia is the most common electrolyte disorder encountered in clinical medicine [3]. Incidence rates as high as 15%–22% have been reported in hospitalized patients in intensive care units [4] or long-term care facilities [5]. However, most studies have reported a hospital-based incidence of 1%–4% for more clinically significant cases of hyponatremia (i.e., serum [Na^+] less than 130 mEq/L) [3]. There are no published estimates of the prevalence of hyponatremia in the U.S. Miller, Morley, and Rubenstein [6] reviewed medical charts for 119 nursing home patients and found that 53% had at least one episode of hyponatremia over a one-year period. More recently, Hawkins [7] examined the prevalence of hyponatremia in 120,137 patients at initial presentation to healthcare providers in Singapore, and reported a range from 7.2% in the community care setting to as high as 28.2% for acute care hospitalized patients.

Hyponatremia has also been associated with negative outcomes in many chronic diseases, most notably in patients with congestive heart failure [8]. One study of 161 patients with severe congestive heart failure found hyponatremia to be a significant predictor of cardiovascular mortality, with 69% of hyponatremic patients dying within 24 months as compared with 40% of patients without baseline hyponatremia ($P < 0.001$) [9]. Results from a prospective study of 435 hospitalized patients with congestive heart failure indicated that a serum [Na^+] less than or equal to 135 mEq/L was a significant ($P < 0.01$) and independent predictor of major complication or death during hospitalization; 25% of patients with a serum [Na^+] less than or equal to 135 mEq/L, versus 15% of those with a serum [Na^+] greater than 135 mEq/L experienced a major complication or died [10]. Similarly, in a study examining admission hyponatremia among 4,123 geriatric patients, in-hospital mortality was 16% among patients with admission hyponatremia versus 8% among those without this condition [11]. And in a general adult hospitalized population, Anderson et al. [12] found that mortality rates were 60-fold higher in patients with even asymptomatic hyponatremia compared to normonatremic patients. The degree to which this strong association between hyponatremia and negative outcomes is causally related to the hyponatremia, and might be improved with more effective therapies, is not known.

There is limited information in the literature about health care resource use and costs attributable to the effects of hyponatremia. This may be due to the low incidence of clinically significant hyponatremia, or due to methodological challenges of isolating the effects of the condition since morbidity and mortality are often related to the underlying medical disorder. Two studies in patients with congestive heart failure have determined that hyponatremia is a significant predictor of increased length of stay[10,13]. To our knowledge, no studies have been conducted assessing the cost of illness of hyponatremia in different treatment settings. Such information would be useful given the likely variation in intensity of resource use and costs of care associated with hyponatremia.

Against this background, the present study utilized a prevalence-based cost-of-illness framework to estimate the annual cost of illness of hyponatremia in the U.S. The analysis incorporates data from publicly available databases, published literature, and an expert physician panel. The resulting cost of illness estimate is presented from the payor perspective and focuses on direct treatment costs, while excluding indirect costs (i.e., worker productivity losses) that may be associated with hyponatremia.

Methods

We used a prevalence-based epidemiologic model to estimate the annual direct costs of hyponatremia in the U.S. [14]. A differential approach was used; to focus on the excess burden of hyponatremia, costs related to any diagnosis or underlying disease other than hyponatremia were not taken into account [15]. The two main sources of data for the analysis were the published literature and an expert panel. Indirect costs were not included in the analysis as the expert panel did not feel qualified to assign levels of work loss or caregiver burden based on the presence of hyponatremia.

Expert panel

Expert opinion was used in this study because neither the published literature nor national surveys or databases contain adequate information on the health care resource use and costs associated with hyponatremia. The role of the expert panel was two-fold: first, to provide a classification scheme for hyponatremia patients, and second, to estimate the health care resource use associated with the diagnosis and treatment of hyponatremia.

Our goal was to choose physicians who are representative of the types of physicians who encounter hyponatremia in practice, and are considered experts in the field [16]. An endocrinologist was chosen as lead physician based on a review of the published hyponatremia literature. The lead physician then provided recommendations for other panel members with an extensive background and experience in treating patients with hyponatremia. The expert panel was comprised of six physicians from different spe-

cialties, including two endocrinologists, one nephrologist, one cardiologist, one internist, and one intensivist.

A consensus panel was utilized to estimate desired model parameters for patients with hyponatremia [17]. This approach was utilized by Murray et al. in their study of the cost of refractory epilepsy [18], and by Plumb and Guest in their analysis of the cost of erectile dysfunction in the UK [19]. A detailed questionnaire was mailed to panel members in advance of a face-to-face meeting. The panel members completed the questionnaire prior to the meeting and the responses were summarized and presented to the panel on the day of the meeting. The questionnaire results and other issues were then discussed among the panel members until agreement was reached. Previous research has found that consensus panel decisions have a high degree of consistency and validity when compared to clinical practice [20,21].

The questionnaire covered the following topic areas: classification of hyponatremia patients, health care resource use associated with the diagnosis of hyponatremia, initial treatment settings for hyponatremia, health care resource use associated with the treatment of hyponatremia, and the treatment of hyponatremia-related complications.

Classifying hyponatremia patients

The first step in establishing the economic burden of a given disease or condition is to characterize the patient population with the condition. The expert panel was asked to provide a classification scheme for hyponatremic patients that correlated well with the levels of health care resource use. For example, if there were two main types of hyponatremic patients, and one type never used health care services while the other type had frequent hospitalizations, this distinction would be critical for an economic evaluation. Four classification options were presented to the panel including: 1) acute [developing within 48 hours] vs. chronic [unknown duration or duration greater than 48 hours] hyponatremia, 2) symptomatic vs. asymptomatic hyponatremia, 3) a combination of the first two options (i.e., acute symptomatic, acute asymptomatic, chronic symptomatic, chronic asymptomatic), or 4) based on underlying condition (e.g., congestive heart failure, syndrome of inappropriate antidiuretic hormone secretion [SIADH]). The panel agreed unanimously to base the economic evaluation on the third option.

The panel was not able to provide a specific percentage breakdown of hyponatremia patients into the four categories, but did provide a range of percentages for each category. For the purposes of estimating the cost of illness of hyponatremia, we utilized an approach similar to the one used by Severens et al in their analysis of the cost of pressure ulcers in the Netherlands whereby the ranges provided by the expert panel were converted into "low" and "high" estimates [22] (described in greater detail below).

Estimating prevalence of hyponatremia

The ability to estimate the prevalence of hyponatremia in the U.S. population was enabled by the availability of two key data elements. First, publicly available hospital discharge data provided empirical evidence of how many patients are treated for hyponatremia in an inpatient setting each year in the U.S. The U.S. Government's Healthcare Cost & Utilization Project (HCUP) database contains hospital discharge data from a 20% sample of U.S. hospitals (approximately 7 million hospital stay records from 1,000 hospitals in 33 states) and yields nationally representative estimates of inpatient care [23]. In 2002 there were an estimated 923,473 hospital stays with either a principal or secondary discharge diagnosis of hyponatremia (ICD-9-CM diagnosis code 276.1). We assumed an average of 1.25 hospital stays per patient, based on a study by Tierney et al. [24] which reported 954 admissions for the 763 hyponatremic patients in their sample, to arrive at an estimated 738,778 patients treated for hyponatremia in an inpatient setting in the U.S.

Second, using the four-level classification system, the expert panel provided "low" and "high" estimates of the proportion of hyponatremic patients who are treated; and "low" and "high" estimates of the proportion initially treated in an inpatient setting (Table 1). All possible combinations of the three sets of low and high estimates in Table 1 (e.g., one combination would include the "low" estimate for classification, the "low" estimate for percentage treated, and the "low" estimate for percentage treated as inpatient) were evaluated and resulted in eight separate estimates of the proportion of all hyponatremic patients who are treated in an inpatient setting. Based on these calculations, we were able to extrapolate from the number of "known" hospitalized hyponatremia patients (i.e. 738,778 patients) to produce eight separate estimates of the total number of persons with hyponatremia in the U.S.

The following example using the "low" values for each of the three parameters illustrates our methodology for calculating the prevalence estimate. In this scenario, for every 100,000 individuals with hyponatremia, 1,000 (1%) are acute and symptomatic. Of those, 900 are treated (90%), and 585 (65% of those treated) are treated in an inpatient setting. By adding the 585 acute and symptomatic patients to the similarly derived values for the acute asymptomatic, chronic symptomatic, and chronic asymptomatic groups, we determined there were a total of 13,455 patients treated for hyponatremia in an inpatient setting for every 100,000 individuals with hyponatremia. Given that an estimated 738,778 patients were treated in an inpatient

Table 1: Expert panel estimates used in prevalence calculations

Classification of hyponatremia patients	**Low**	**High**
Acute and symptomatic	1%	1%
Acute and asymptomatic	4%	4%
Chronic and symptomatic	20%	15%
Chronic and asymptomatic	75%	80%
	100%	100%
Percent of hyponatremia patients treated	**Low**	**High**
Acute and symptomatic	90%	100%
Acute and asymptomatic	90%	100%
Chronic and symptomatic	66%	85%
Chronic and asymptomatic	10%	20%
Of those treated, percent treated initially as inpatient	**Low**	**High**
Acute and symptomatic	65%	75%
Acute and asymptomatic	65%	75%
Chronic and symptomatic	40%	45%
Chronic and asymptomatic	70%	80%

setting in 2002, the total number of individuals with hyponatremia in the U.S. using this particular combination of estimates was 5.49 million (738,778 × [100,000/13,455]).

We repeated this procedure for all eight possible combinations of estimates (e.g. "low", "high", "low"; "high", "high", low"). The lowest and highest of the eight resulting prevalence estimates were then used in subsequent cost of illness calculations (i.e., "low" scenario and "high" scenario).

While hyponatremia is defined as a serum sodium concentration ([Na^+]) less than 135 mEq/L [1], the panel felt that a serum sodium concentration ([Na^+]) less than 130 mEq/L is the threshold for clinically significant hyponatremia, and therefore the level physicians would consider the threshold for initiating treatment. Accordingly, the expert panel's estimates of treatment patterns, and therefore our estimates of prevalence, were based on a conservative assumption that only patients with clinically significant hyponatremia (serum sodium concentration ([Na^+]) less than 130 mEq/L) are being treated.

Estimating health care resource use

To simplify the costing exercise, the panel first reached consensus on a mutually exclusive list of initial treatment settings for patients with hyponatremia, and low and high estimates for the percentage of patients treated in each setting: inpatient, emergency room (ER) (without being hospitalized), or doctor's office (without being hospitalized or visiting the emergency room) (Table 2). For those admitted as an inpatient, the panel estimated the proportion admitted specifically for hyponatremia; and the average, incremental increase in length of stay due to hyponatremia for patients admitted due to other conditions. The panel provided detailed information on the hyponatremia-related tests and procedures that are performed in each treatment setting, and the proportion of patients receiving each test or procedure. This included both diagnostic and therapeutic tests and procedures. The frequency and resource use intensity of follow-up visits were also estimated by the panel. The panel's estimates of the proportion of patients receiving each test and procedure performed at the initial evaluation varied depending on the patient's underlying condition (Table 3). Differences in the tests and procedures performed were based on whether the patient's etiology was: 1) SIADH; 2) congestive heart failure, cirrhosis, renal failure, or diuretics; or 3) any other etiology. The panel provided estimates of the percentage of hyponatremia patients who fell into each of the three etiological categories. These percentages enabled us to calculate an absolute number of patients receiving each test and procedure by underlying condition at initial evaluation. Estimates of the proportion of patients receiving each test and procedure performed at follow-up were based on the initial treatment setting. The number of patients receiving each test and procedure at initial evaluation and follow-up were multiplied by unit prices to determine the contribution of tests and procedures to the total cost of illness.

Table 2: Treatment by setting for hyponatremia patients

	Inpatient	ER	Office/Clinic
Low Scenario (3.16 million prevalence; 1.17 million treated patients)			
Overall	**63% (738,778)**	**24% (280,988)**	**13% (148,387)**
Acute and Symptomatic	75% (23,679)	25% (7,893)	0% (0)
Acute and Asymptomatic	75% (94,715)	25% (31,572)	0% (0)
Chronic and Symptomatic	45% (241,524)	45% (241,524)	10% (53,672)
Chronic and Asymptomatic	80% (378,861)	0% (0)	20% (94,715)
High Scenario (6.07 million prevalence; 1.35 million treated patients)			
Overall	**55% (738,778)**	**25% (333,070)**	**20% (274,036)**
Acute and Symptomatic	65% (35,530)	35% (19,131)	0% (0)
Acute and Asymptomatic	65% (106,590)	35% (57,394)	0% (0)
Chronic and Symptomatic	40% (256,544)	40% (256,544)	20% (128,272)
Chronic and Asymptomatic	70% (340,115)	0% (0)	30% (145,764)

Again, the panel provided a range of estimates for many of the resource use items. Therefore, when calculating the cost of illness based on the "low" prevalence scenario, we utilized the low end of the range of resource use estimates from the expert panel, and vice versa for the "high" prevalence scenario. This approach resulted in both the most conservative and most generous cost of illness estimates.

The questionnaire also addressed neurological complications due specifically to hyponatremia. However, the panel agreed that given how infrequently these arise, they could not provide an accurate estimate of the percentage of patients who would incur costs for complication-related resource use. In the rare cases in which a patient does develop complications, costs are substantial; but because the number of patients affected is small and could not be confidently quantified, these costs have not been included in the analysis.

Cost assignment

The cost of care for patients hospitalized specifically for hyponatremia was based on the average costs for hospitalizations with a principal discharge diagnosis of hyponatremia (ICD-9-CM code 276.1) as determined from the U.S. Government's Healthcare Cost & Utilization Project's (HCUP) Nationwide Inpatient Sample (NIS) 2002 database. An average cost-to-charge ratio of 0.53, estimated based on publicly available Medicare cost report data [25], was applied to the total billed charges available in the HCUP; and costs were updated to year 2004 U.S. dollars based on the Consumer Price Index for hospital inpatient services[26] A daily ("per diem") cost obtained from a private hospital discharge database was applied to the incremental days in the hospital due to hyponatremia for patients with other conditions. Physician fees associated with office visits, tests, and procedures were based on national prevailing fees for 2004.[27] Facility fees were based on Medicare's Ambulatory Payment Classification (APC) System[28] Unit costs are provided in Table 4.

Results

Prevalence of hyponatremia in U.S

The prevalence estimates ranged from a low of 3.16 million to a high of 6.07 million persons with hyponatremia in the U.S. on an annual basis. This represents approximately 1.1%–2.1% of the total U.S. population. We found the combination that yielded the lowest prevalence estimate to be the one that used the 'low' classification estimates (prevalence distributed as 1% acute and symptomatic, 4% acute and asymptomatic, 20% chronic and symptomatic, and 75% chronic and asymptomatic), the 'high' percentage treated estimates (100% for acute and symptomatic, 100% for acute and asymptomatic, 85% for chronic and symptomatic, and 20% for chronic and asymptomatic), and the 'high' percentage treated inpatient estimates (75% for acute and symptomatic, 75% for acute and asymptomatic, 45% for chronic and symptomatic, and 80% for chronic and asymptomatic). Using this combination of estimates, we calculated that 23,400 patients are treated for hyponatremia in an inpatient setting for every 100,000 individuals with hyponatremia. Based on the 2002 estimated total of 738,778 patients treated for hyponatremia in an inpatient setting, this places the overall U.S. prevalence at 3.16 million.

The combination that yielded the highest prevalence estimate was the one that used the 'high' classification esti-

Table 3: Unit costs

Resource Item	Office	ER/Inpatient	
	Professional Fee	Professional Fee	Facility Fee/Lab Fee
Office and ER Costs			
Initial Visit	$110.50	$130.77	$157.50
Follow-up visit	$71.00	N/A	N/A
Chest X-Ray	$122.00	$42.57	$55.50
MRI	$1,852.50	$388.28	$382.00
Chest CT	$1,067.50	$320.68	$352.00
Abdominal CT	$923.00	$253.94	$281.50
Urine osmolality	$31.00	$31.00	$9.52
TSH	$66.00	$66.00	$23.47
ACTH stimulation test	$159.50	$159.50	$53.97
Basic metabolic panel	$39.50	$39.50	$11.83
Venipuncture			$3.00
Inpatient costs			
Patients admitted for hyponatremia			
Total cost of hospital stay			$6,926.00
Patients admitted for another condition			
Per diem (general ward)			$500.00
Per diem (ICU)			$1,100.00
Consultation		$106.00	

mates (prevalence distributed as 1% acute and symptomatic, 4% acute and asymptomatic, 15% chronic and symptomatic, and 80% chronic and asymptomatic), the 'low' percentage treated estimates (90% for acute and symptomatic, 90% for acute and asymptomatic, 66% for chronic and symptomatic, and 10% for chronic and asymptomatic), and the 'low' percentage treated inpatient estimates (65% for acute and symptomatic, 65% for acute and asymptomatic, 40% for chronic and symptomatic, and 70% for chronic and asymptomatic). Based on this combination of estimates, 12,164 patients are treated for hyponatremia in an inpatient setting for every 100,000 individuals with hyponatremia. This places the overall U.S. prevalence at 6.07 million.

Treatment by setting

Table 2 provides a breakdown of the number and percentage of treated hyponatremia patients who receive initial treatment in each setting of care. Estimates are provided for both the low and high prevalence scenarios. The expert panel agreed that a low percentage of patients with hyponatremia would be treated solely in the office/clinic setting, and that chronic asymptomatic patients would not be seen in the ER. Chronic hyponatremia was estimated to account for greater than 80% of patients initially treated in an inpatient setting, greater than 85% of patients initially treated in an ER, and generally all patients initially treated in an office/clinic setting. Overall, 55%–63% of persons with hyponatremia who are treated are estimated to receive their initial treatment in an inpatient setting, 25% are estimated to be treated initially in the emergency room, and 13%–20% are treated solely in the office setting.

There are an estimated 1 million hospitalizations per year in the U.S. with a principal (accounting for 6.6% of the stays) or secondary discharge diagnosis of hyponatremia. Of all patients with hyponatremia in the inpatient setting, it was estimated that 4%–8% were admitted specifically for hyponatremia and 58%–67% required a longer length of stay due to symptomatic hyponatremia, depending upon the low or high prevalence scenario. The estimate of the total number of additional days of hospitalization due to hyponatremia as a comorbid condition ranged from 497,000 to 4.5 million days per year.

Cost of illness

The direct costs of treating hyponatremia in the U.S. on an annual basis were estimated to range between $1.6 billion (based on the low prevalence scenario) and $3.6 billion (using the high prevalence scenario) (Table 5). Hospitalization costs (including readmissions) accounted for approximately 70% of the total cost of illness. For the 738,778 patients treated in an inpatient setting, hospitalization costs were estimated at $1.1 billion, or $1,528 per patient (low prevalence scenario), to $2.5 billion, or $3,441 per patient (high prevalence scenario). Hospitalization costs for the subset of patients who were admitted not specifically for hyponatremia but for another reason were based strictly on the days their hospital stay was

Table 4: Diagnostic tests and procedures

	Chest X-Ray	Basic Metabolic Panel	TSH	Urine Osmolality	ACTH Stimulation Test	MRI	Chest CT with or without Abdominal Scan
Initial Evaluation							
Patients with CHF, Cirrhosis, Renal Failure, or Taking Diuretics	100%	100%	100%	0%	0%	0%	0%
Patients with SIADH	100%	100%	100%	100%	100%	25%	25%
Patients with All Other Etiologies	100%	100%	100%	100%	100%	0%	0%
Follow-Up Visits							
Initial Treatment in Inpatient Setting	100%	100%	0%	0%	0%	0%	0%
Initial Treatment in ER Setting	100%	100%	0%	0%	0%	0%	0%
Initial Treatment in Office Setting	80%–90%	90%	0%	0%	0%	0%	0%

extended due to their hyponatremia. Therefore, the estimated costs for these patients can be attributed solely to the hyponatremia and are independent of any underlying comorbid condition that was their primary reason for admission. Admissions specifically for hyponatremia accounted for approximately 20% of the hospitalization costs, with the remaining 80% attributable to patients admitted for another condition but whose length of stay was extended due to hyponatremia. Follow-up treatment was the second largest cost driver, accounting for 15%–20% of total costs, depending upon the prevalence scenario. In the low prevalence scenario, 577,131 patients were estimated to require follow-up treatment at a cost of $263 million, or $456 per patient. In the high prevalence scenario, the cost for the 754,861 patients requiring follow-up treatment was estimated at $693 million, or $918 per patient.

Discussion

This study indicates that hyponatremia represents a substantial medical and economic burden in the U.S. There are approximately 1 million hospitalizations per year in the U.S. with a principal or secondary discharge diagnosis of hyponatremia, as well as an estimated 105,000 to 120,000 annual ER visits, and 1.4 million to 3.4 million annual office visits for hyponatremia. The cost of illness

Table 5: Per patient and total costs of care by treatment setting

	Total # of patients	$ per patient	Total costs
Low Prevalence Scenario			
Initial treatment in inpatient setting	738,778	$1,069	$789,604,595
Initial treatment in ER	177,063	$587	$103,950,219
Initial treatment in office setting	148,279	$1,049	$155,513,136
Follow-up treatment	473,097	$453	$214,332,436
Total			**$ 1,263,400,385**
High Prevalence Scenario			
Initial treatment in inpatient setting	738,778	$2,721	$2,009,973,806
Initial treatment in ER	234,749	$381	$89,464,969
Initial treatment in office setting	257,305	$1,057	$271,952,427
Follow-up treatment	639,810	$916	$585,770,794
Total			**$ 2,957,161,995**

estimate of $1.6 billion to $3.6 billion for hyponatremia can be put into perspective by reviewing published direct cost estimates for other conditions (updated to Year 2004 US $), including $788 million for treating children with respiratory syncytial virus [29], $1.5 billion for treating refractory epilepsy in adults [18], $2.3 billion for treating hay fever [30], $23.4 billion for treating urinary incontinence [31], and $23.7 billion for congestive heart failure [32].

There have been no previously published estimates of the total direct costs of treating hyponatremia, but several previous studies corroborate the conclusions of our analysis. Results from a prospective study of 435 patients admitted to a university hospital with evidence of congestive heart failure showed that hyponatremia (defined as serum [Na^+] less than or equal to 135 mEq/L) was significantly ($P \leq 0.01$) and independently associated with an increased duration of hospital stay and higher hospital cost [10]. The increased length of hospital stay in patients with hyponatremia was demonstrated in another retrospective analysis of 1,046 patients (58% older than 65 years) hospitalized for heart failure [13]. In this study, 171 patients had hyponatremia (defined as serum [Na^+] less than 135 mEq/L) at admission and their mean length of stay was 5.78 days, versus 4.72 days among patients without hyponatremia ($P = 0.0001$). The only variable other than hyponatremia that was associated with a longer duration of hospitalization in this study was admission from a skilled nursing facility (6.22 days). A multivariate linear regression analysis indicated that hyponatremia was a significant predictor of hospitalization duration in this cohort of patients.

The current study's cost of illness estimate for hyponatremia is most likely a conservative one. The prevalence estimate was based in large part on the number of hospitalizations for hyponatremia as recorded (by ICD-9-CM diagnosis code) in a national database, but there is evidence that the ICD-9-CM code for hyponatremia represents only one-third of the patients admitted to the hospital and experiencing hyponatremia, due to the low sensitivity (30%) of the diagnosis code [33]. In addition, a high proportion of hyponatremia in the hospital setting is iatrogenic [12,34] and hospitals may be reluctant to include the code in the discharge data.

More definitive resource use and cost data from longitudinal, patient-level databases would have been preferred. However, as noted above, existing databases have their own inherent weaknesses due to the lack of sensitivity with the ICD-9-CM diagnosis code for hyponatremia. Future studies should therefore consider a broader national survey of treatment patterns and resource use associated with hyponatremia.

There are additional limitations associated with this analysis. Although previous research has found that consensus panel decisions have a high degree of consistency and validity when compared with clinical practice [20,21] the panel estimates in the current study are uncertain. A variety of formal and informal methods have been developed for use as consensus-building techniques in group decision-making [35]. The consensus development process in this study was a variation of a modified Delphi panel. In the first stage of a two-stage process, participants privately completed a mailed questionnaire. In the second stage, their compiled responses were presented at a face-to-face meeting where the group engaged in open communication to discuss any variations in their responses. The panel members reached consensus as a group on an appropriate estimate for each question, often in the form of a range. Unlike a true Delphi panel where participants never meet directly, a noted strength of the interactive forum is the opportunity the participants have to provide information, insight, and rationales for their responses. However, a limitation of this approach is the potential for decisions to be reached by persuasion rather than consensus due to an influential member of the group. While no single member of the panel in this study appeared to dominate the consensus process, we recognize that social forces such as persuasion and conformity may have influenced panel members' final decisions.

Additional uncertainty in the panel's estimates lay in the subjective nature of their responses. Previous commentaries in the literature have suggested the potential for bias in prevalence estimates provided by practicing clinicians because their experience is based on the duration of illness, severity, and other clinical characteristics of patients who receive treatment [36]. For example, the prevalence of severe and symptomatic hyponatremia may be easier to estimate than the number of patients who have undetectable symptoms. We believe we minimized this potential bias by having a cross-disciplinary panel familiar with the variety of ways hyponatremia can present itself (i.e. acute, chronic, symptomatic, asymptomatic).

Another study limitation is the lack of inclusion of costs associated with complications of hyponatremia, which although rare, can be substantial. The panel felt it would be difficult to quantify the complications for the extremely small percentage of patients who experience these events. Resource use and costs associated with complications vary depending on the nature and severity of the complication. Furthermore, many complications of hyponatremia are neurological with severe long-term sequelae. Therefore, an accurate assessment of the economic burden would have to include direct and indirect costs incurred over time, which would vary depending on several patient, clinical, and treatment factors. Given the

high degree of uncertainty associated with estimating the economic impact of complications and the low percentage of patients involved, the panel deemed it most appropriate to exclude complications from the analysis.

The analysis also did not include the indirect costs associated with hyponatremia. The expert panel did not feel qualified to assign levels of work loss or caregiver burden based on the presence of hyponatremia; and there were no data sources available to directly link hyponatremia with work loss. The increased mortality risk that has been linked to hyponatremia [9,10,37] was assumed to apply mostly to non-working elderly populations, and thus the productivity losses due to mortality were considered minimal.

This analysis of the economic impact of hyponatremia raises a number of clinical implications that have not been fully appreciated nor discussed regarding this disorder. The clinical importance of symptomatic hyponatremia has been well appreciated by clinicians over the past decade, both as a result of the morbidity and mortality associated with hyponatremic encephalopathy, as well as that associated from the production of pontine and extrapontine myelinolysis from overly rapid correction of severe hyponatremia [38]. However, both of these situations are relatively rare in terms of overall incidence, likely representing 1% or less of all hyponatremic patients (Table 1). While these dramatic cases have appropriately received much attention in the medical literature, they represent only a small fraction of the resource utilization and costs associated with hyponatremia. Rather, the bulk of the costs attributable to hyponatremia appear to result from a combination of inpatient hospitalization costs (70%) and subsequent follow-up evaluation and treatment (15%–20%), and 80% of these are attributable to those patients for whom hyponatremia was not the primary diagnosis. Thus, these relatively conservative estimates suggest that more than two-thirds of the cost of hyponatremia occurs from patients hospitalized for other conditions whose length of hospital stay is then extended due to coincident hyponatremia. Further analysis of the reasons underlying this observation is therefore indicated.

Several possibilities can potentially explain this association. First, hyponatremia may be a marker of the severity of the underlying disease, in which case hospitalizations are longer simply because the hyponatremic patients represent a sicker cohort of all those with the underlying disorder. Second, hyponatremia may add its own complications to those of the underlying disorder, thereby acting as an independent factor that extends the length of hospital stay due to the intrinsic complications of this disorder. Third, the presence of hyponatremia may limit or otherwise compromise optimal treatment of the underlying disorder. Finally, because newly-discovered hyponatremia represents a metabolic abnormality of uncertain etiology and significance, the medical evaluation required to ascertain the underlying cause of the hyponatremia will necessarily involve investment of additional time and resources. Each of these possible explanations will be considered in greater detail.

Hyponatremia has long been known to occur in association with a variety of underlying conditions, from tumors that synthesize and excrete arginine vasopressin ectopically [39] to disorders such as congestive heart failure and cirrhosis where arginine vasopressin secretion from the posterior pituitary is stimulated by decreased effective circulating blood volume [40]. It is striking that mortality rates have been found to be significantly higher in hyponatremic patients across a broad range of primary disorders, including congestive heart failure and acute myocardial infarctions [41], pulmonary tuberculosis [42], and childhood diarrhea [43]. Perhaps the strongest data for hyponatremia as a marker of disease severity comes from multiple studies of patients with congestive heart failure, which have clearly shown that hyponatremia represents an independent risk factor in patients with heart failure [8], nearly doubling the risk of mortality in this group [44,45]. Most evidence suggests that this association reflects the underlying pathophysiology of the heart failure (i.e., that hyponatremia is a marker of severity of the underlying disease). This is partly based upon the findings that arginine vasopressin is one of the hormones stimulated during the activation of multiple neurohumoral systems that occurs in association with progression of the heart failure. In the SOLVD (Studies of Left Ventricular Dysfunction), subjects with left ventricular dysfunction had significantly higher plasma arginine vasopressin levels compared to controls, and arginine vasopressin levels were highest in the subjects with overt heart failure [46]. While these data support the possibility that case hospitalizations are longer in hyponatremic patients because they represent a sicker cohort of all patients with the underlying disorder, there are a number of reasons to suggest that the elevated plasma arginine vasopressin levels associated with hyponatremia may in fact aggravate disease progression in patients with heart failure. Specifically, the excess water retention caused by arginine vasopressin may cause worsening of congestive heart failure due to diastolic wall stress from the intravascular volume expansion that is caused by the excess retained water; in addition, the elevated arginine vasopressin levels may lead to increased systolic wall stress as a result of arteriolar vasoconstriction produced by activation of vasopressin V1a receptors in the vasculature, and potential stimulation of myocardial hypertrophy because of growth-stimulating effects of vasopressin V1a receptors in the heart. Thus, the assumption that hyponatremia due

to increased arginine vasopressin levels is simply a marker of the severity of the underlying left ventricular dysfunction in patients with congestive heart failure rather than a causal factor in the increased mortality of this subgroup has never been directly tested and remains a presumption.

Regardless of whether elevated arginine vasopressin levels and hyponatremia directly contribute to the morbidity and mortality of underlying primary diseases, there is little question that the presence of hyponatremia can and often does interfere with the treatment of underlying diseases through multiple mechanisms. Perhaps most importantly, standard therapy for euvolemic and hypervolemic patients with hyponatremia is fluid restriction in order to prevent further water retention and worsening of the hyponatremia. This necessity can limit therapies that involve concomitant fluid administration to patients, including antibiotic therapy, chemotherapy, and parenteral nutrition. Furthermore, hyponatremic patients with edema-forming diseases such as congestive heart failure and cirrhosis who require aggressive diuresis of retained water and sodium sometimes do not receive as large a dose of diuretics as otherwise might be given because of fears of worsening hyponatremia as a result of the natriuresis produced by conventional diuretic agents. In each case, this would result in prolonging the period to reach the medical endpoint of the hospitalization.

Finally, even if none of the above scenarios apply to a specific case, the current standard of care for newly diagnosed hyponatremia is to ascertain the etiology of the hyponatremia before ascribing it to the underlying disease [47]. This requires a combination of both laboratory and radiological testing (Table 3) that can add several days to hospitalization, or alternatively, the employment of these resources during follow-up visits. In many cases underlying etiologies are not found,[48] raising questions about the efficacy of the minimum diagnostic evaluation that is appropriate for all cases of hyponatremia.

While no study to date has definitively ascertained among the various possible reasons that account for the increased length of stay in patients with coincident hyponatremia, it seems likely that all of the factors postulated as potential causes of increased resource utilization contribute to this occurrence to varying degrees in individual cases.

Conclusion

In conclusion, approximately 70% of the estimated $1.6 billion to $3.6 billion cost of illness for hyponatremia is attributable to costs incurred in an inpatient setting. The majority of these costs are attributable to the incremental resource utilization for patients who were not admitted specifically for hyponatremia, but whose hospitalization was prolonged due to hyponatremia. While the potential causes for this are multiple and difficult to ascertain with any degree of certainty, it seems likely that newer therapies that may reduce the incidence and severity of hyponatremia in the inpatient setting could minimize the costs of this important clinical disorder.

Abbreviations

Abbreviation Description

APC Ambulatory Payment Classification System

ER emergency room

HCUP Healthcare Cost & Utilization Project

Na^+ serum sodium concentration

NIS Nationwide Inpatient Sample

SIADH syndrome of inappropriate antidiuretic hormone secretion

SOLVD Studies of Left Ventricular Dysfunction

Competing interests

This study was funded by Yamanouchi Pharma America, Inc., Paramus, New Jersey.

Authors' contributions

Audra Boscoe and Clark Paramore contributed to the conceptual design, collected data, conducted the analyses, and drafted the manuscript. Joseph Verbalis contributed to the conceptual design and provided critical revision of the manuscript for important intellectual content.

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Nagler et al. BMC Medicine 2014, 12:231
http://www.biomedcentral.com/1741-7015/12/231

BMC Medicine

RESEARCH ARTICLE Open Access

Diagnosis and treatment of hyponatremia: a systematic review of clinical practice guidelines and consensus statements

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Abstract

Background: Hyponatremia is a common electrolyte disorder. Multiple organizations have published guidance documents to assist clinicians in managing hyponatremia. We aimed to explore the scope, content, and consistency of these documents.

Methods: We searched MEDLINE, EMBASE, and websites of guideline organizations and professional societies to September 2014 without language restriction for Clinical Practice Guidelines (defined as any document providing guidance informed by systematic literature review) and Consensus Statements (any other guidance document) developed specifically to guide differential diagnosis or treatment of hyponatremia. Four reviewers appraised guideline quality using the 23-item AGREE II instrument, which rates reporting of the guidance development process across six domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Total scores were calculated as standardized averages by domain.

Results: We found ten guidance documents; five clinical practice guidelines and five consensus statements. Overall, quality was mixed: two clinical practice guidelines attained an average score of >50% for all of the domains, three rated the evidence in a systematic way and two graded strength of the recommendations. All five consensus statements received AGREE scores below 60% for each of the specific domains.
The guidance documents varied widely in scope. All dealt with therapy and seven included recommendations on diagnosis, using serum osmolality to confirm hypotonic hyponatremia, and volume status, urinary sodium concentration, and urinary osmolality for further classification of the hyponatremia. They differed, however, in classification thresholds, what additional tests to consider, and when to initiate diagnostic work-up. Eight guidance documents advocated hypertonic NaCl in severely symptomatic, acute onset (<48 h) hyponatremia. In chronic (>48 h) or asymptomatic cases, recommended treatments were NaCl 0.9%, fluid restriction, and cause-specific therapy for hypovolemic, euvolemic, and hypervolemic hyponatremia, respectively. Eight guidance documents recommended limits for speed of increase of sodium concentration, but these varied between 8 and 12 mmol/L per 24 h. Inconsistencies also existed in the recommended dose of NaCl, its initial infusion speed, and which second line interventions to consider.

Conclusions: Current guidance documents on the assessment and treatment of hyponatremia vary in methodological rigor and recommendations are not always consistent.

Keywords: Clinical practice guideline, Hyponatremia, Systematic review

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Background

Hyponatremia is the most common electrolyte disorder in clinical medicine; it represents an excess of water relative to total body solute [1]. Hyponatremia usually results from the intake and subsequent retention of electrolyte-free water in response to true hypovolemia due to gastrointestinal solute loss or malnutrition; decreased effective circulating volume due to heart failure or liver cirrhosis; or non-osmotic vasopressin activity due to malignancies, infections, medications, pain, or stress [2]. When defined as a serum sodium concentration below 135 mmol/L, hyponatremia occurs in up to 8% of the general population and in up to 60% of hospitalized patients [2,3]. Acute profound hyponatremia can cause brain edema, but also chronic mild hyponatremia is associated with poor health outcomes. Even when comorbid conditions are taken into account, people with a mildly decreased serum sodium concentration have a 30% higher risk of death and are hospitalized 14% longer relative to those without hyponatremia [2,4].

Despite the frequency and severity of some of the associated complications, research suggests hyponatremia is often neglected by clinicians [5]. If acquired in hospital, it may take days before the electrolyte disorder is investigated, potentially allowing a further decrease in serum sodium concentration and exposing patients to the dangers of profound hyponatremia. When efforts are made to explore the underlying cause, clinicians use widely different strategies for differential diagnosis, testing is often inadequate and misclassification of the hyponatremia frequently occurs [6,7].

Hyponatremia may be managed clinically by different specialists, such as endocrinologists, nephrologists, geriatricians, or intensivists, and, accordingly, management strategies often vary [5]. Although probably related to variation in awareness, differences in expert opinion on whom and how to treat only add to the confusion over optimal management. For instance, although experts agree that acute symptomatic hyponatremia should be treated with hypertonic saline, the optimal concentrations and methods for determining initial infusion speeds are debated [1]. In addition, the risk of osmotic demyelination syndrome after rapid correction of hyponatremia has fuelled intense debate among experts on whether complications of untreated hyponatremia or complications of treatment pose the greatest risk [8]. As different specialist physicians deal with hyponatremia, consultation of different information and guidance sources may add to the variability in treatment seen in clinical practice today.

Clinical practice guidelines and consensus statements provide recommendations to help evidence-based practice by suggesting the most appropriate diagnostic tests and the most appropriate treatments. Over the years, multiple organizations have developed recommendations to assist clinicians in the management of hyponatremia. To be reliable, these recommendations must be based on a systematic review of the evidence, and have a transparent and multidisciplinary development process [9]. Inconsistencies between recommendations may arise from failing to meet development standards and can only add to unwarranted variability in management. In this study, we aimed to explore the scope, content, and consistency of the existing guidance documents on the diagnosis and management of hyponatremia in adults and children.

Methods

Criteria for selection of studies

We included evidence-based clinical practice guidelines and consensus statements on the diagnosis and treatment of hyponatremia. We defined clinical practice guidelines as statements that included recommendations intended to optimize patient care informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [9]. We defined consensus statements as documents containing clinically relevant suggestions or recommendations based on the collective opinion of an expert panel [9]. We included all publications independent of language. We excluded guidelines related to the prevention of hyponatremia as well as guidelines relevant to conditions associated with hyponatremia if they were not specifically designed to address hyponatremia. Hence, we excluded guidelines targeting treatment of heart failure, cirrhosis, and cancer unless they were developed with a focus on hyponatremia as a complication. Finally, we also excluded draft unpublished guidelines, conference or discussion papers, personal opinions, and obsolete guidelines replaced by updated recommendations from the same organization.

Search methods for guidelines and consensus statements

We searched MEDLINE (1946 to September Week 1, 2014) and EMBASE (1980 to September 2014), combining vocabulary terms and text words for hyponatremia with terms related to clinical practice guidelines and consensus statements. We also searched guideline databases and websites of organizations as well as of selected professional specialist societies in nephrology, endocrinology, and intensive care medicine. A list of the databases and websites along with the full search strategies are outlined in Additional file 1. EN and JV independently screened the titles and abstracts and discarded those that did not meet the inclusion criteria. Full texts for potentially relevant guidelines or consensus statements were retrieved and examined for eligibility. Both the initial screening and subsequent full-paper assessment stage were completed using Early Review Organizing Software [10].

Data collection process and data items

We developed a draft data extraction form which was piloted and modified as necessary. The extracted data included document characteristics (e.g., year of publication, country/region, development team, funding organization), recommendations related to the diagnosis and assessment of hyponatremia, and recommendations related to the treatment of hyponatremia. EN and JV extracted all data using the standardized data extraction form (Additional file 2) and resolved discrepancies by consensus.

Appraisal of guidelines and consensus statements

Four reviewers independently assessed methodological quality using the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument [11]. AGREE II is an internationally validated, rigorously developed 23-item tool used to evaluate six domains of guideline development: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence [12] (Additional file 3). The AGREE tool has also been used to assess consensus statements [13,14]. The reviewers rated each item on a Likert scale from 1 (Strongly Disagree) to 7 (Strongly Agree). We calculated a total score for each domain by summing up all the scores of the individual items in a domain for each reviewer and then standardizing this total as a percentage of the maximum possible score for that domain, calculated as follows [12]:

$$\frac{Obtained\ \ score - Minimum\ \ possible\ \ score}{Maximum\ \ possible\ \ score - Minimum\ \ possible\ \ score} * 100\%$$

The minimum possible score for each domain equaled the number of questions multiplied by the number of reviewers, multiplied by 1 (strongly disagree). The maximum score for a domain equaled the number of questions multiplied by the number of reviewers, multiplied by 7 (strongly agree). To ensure standardization of each reviewer s approach, all reviewers completed the online training tutorial [15] before starting the project.

In a consensus meeting among the reviewers, we discussed every item for which scores differed by more than 1 point (e.g., 1 versus 3) on the original 7-point scale. Reviewers in turn explained the rationale for their score and had the opportunity to revise their score when they considered this appropriate. We audiotaped the consensus meeting to reliably record the underlying reasons for changing scores.

Synthesis of guideline recommendations

We conducted a textual descriptive synthesis to analyze the scope, content, and consistency of the included recommendations. EN inductively coded the text manually to identify domains covered by the guidelines. These were cross-tabulated with the guidelines and recommendations were inserted into the corresponding cell. For each domain, we compared guideline recommendations to identify similarities and discrepancies. Consistent with the scope of this review, we only tabulated the information on diagnosis and treatment of hyponatremia.

Results

Search results

We identified 1,402 citations, of which we excluded 1,367 after screening titles and abstracts because they did not meet our eligibility criteria (Figure 1). We assessed the full text of the remaining 39 citations and excluded 29 because they were not related to the diagnosis or treatment of hyponatremia, were not clinical practice guidelines or consensus statements, or were guidelines replaced by an updated version (Additional file 4). Ultimately, we included five clinical practice guidelines [16-20] and five consensus statements [21-25]. Six of these documents were retrieved through searching the medical databases [18-20,23-25], the other four through the search of guideline databases and professional society websites [16,17,21,22].

Table 1 shows the general characteristics of the included clinical practice guidelines and consensus statements. Eight national or regional organizations from the Netherlands [16], United Kingdom [17], Northern Ireland [22], Spain [23,25], United States [18,19], Australia [21], and two international groups [20,24] published these guidance documents between 2004 and 2014. One document specifically covered children [21], the others primarily targeted adults. Six groups reported undertaking a systematic review and appraisal of the evidence [16-20,24]. Only three were explicit about the level of evidence that underpinned their recommendations [16,18,20], and only two graded the strength of the guidance recommendations themselves [18,20]. Five guidance documents covered hyponatremia broadly; one specifically covered it in the setting of primary care, one in liver cirrhosis, one in neurosurgery, and one in exercise-associated hyponatremia. Three included treatment only [23-25], the seven others covered diagnosis as well [16-22]. Two groups reported funding by a governmental institution [16,22], one by the professional societies they represented [20]; the others did not report their funding sources [17-19,21,23-25].

Appraisal of guidelines and consensus statements

Figure 2 shows the standardized domain scores for each guideline for each of the six quality domains assessed with the AGREE II tool (See Additional file 5 for mean individual scores per item across reviewers). The overall quality of reporting of the guideline development process as assessed by AGREE varied widely both between guidance documents across domains and within guidance

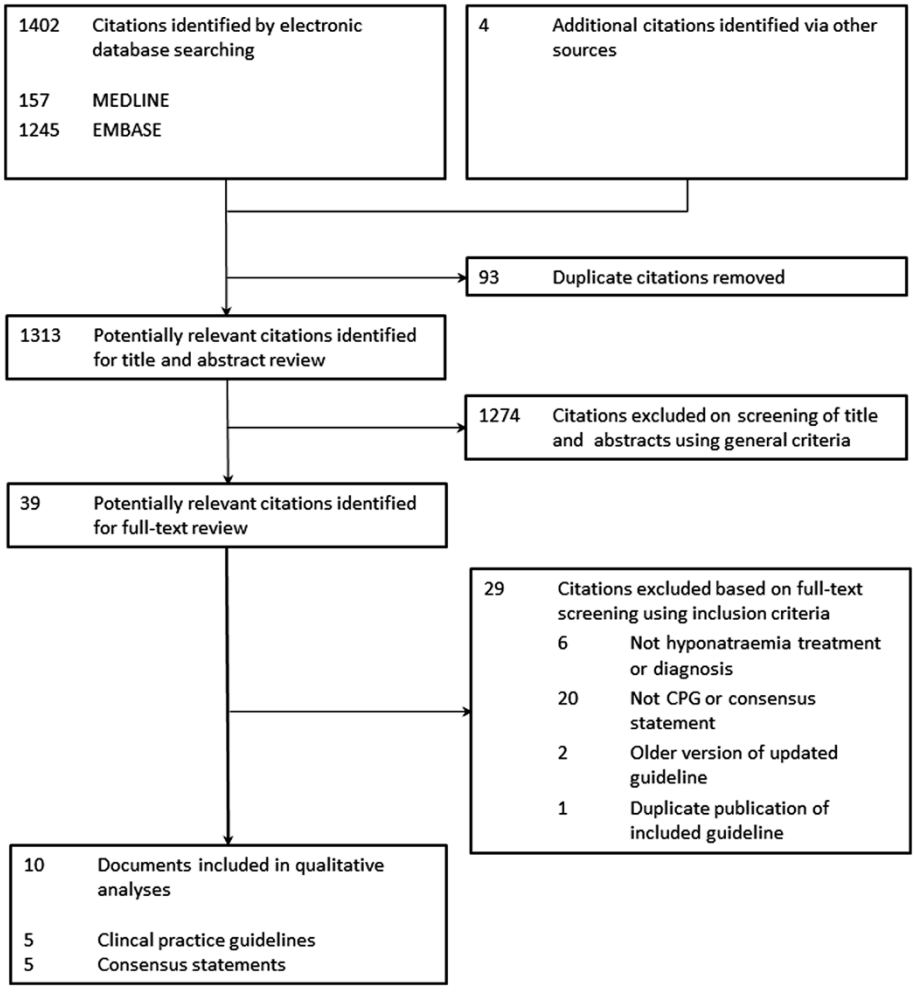

Figure 1 Flow diagram of the identification process for clinical practice guidelines and consensus statements on hyponatremia.

documents between domains. Overall, guideline developers reported the details of the guideline development process only to a limited extent. Most had average scores below 50% in four to six of the six AGREE II domains [17,19,21-25], only two received an average >50% on all six [16,20].

Guidelines received the highest scores for scope and purpose (median 62%; range 28% to 92%) and clarity of presentation (median 47%; range 27% to 75%), and lowest scores for applicability (median 19%; range 10% to 68%) and editorial independence (median 19%; range 2% to 79%).

Initial appraisal results differed more than one point on the Likert scale between two or more reviewers for 143/230 items (62%). The majority of discrepancies were found in the domain Clarity of Presentation, with 90% of items differing more than one point. Group discussion resulted in 287/920 (31%) of individual entries being changed. Finally, no scores differed more than two points and for 82% of items, scores were the same or within one point of each other. Major reasons for changing an entry were a change of own opinion after clarification of the opinion of other reviewers during the group discussion (180/920 entries; 20% entries); aiming for consistency between entries given same available data (39/920; 4%); re-evaluation of the score in light of a noted comment during the appraisal process (30/920; 3%); correction for available data that were overlooked during the initial appraisal (22/920; 2%); misinterpretation of the question during the initial appraisal (6/920; 0.7%); adjusting for arbitrary scoring of items that were felt to be inapplicable for some reason (3/920; 0.3%); adjusting for inconsistent approach to deal with the assumption that a criterion was fulfilled even if this was not clearly mentioned (4/920; 0.4%); and data entry error (3/920, 0.3%). Overall, this resulted in 29/60 (48%) of standardized domain scores being downgraded by a maximum of 10% and 10/60 (17%) of standardized domain scores being upgraded with a maximum of 10%; the remaining 35% remained unchanged.

Table 1 Characteristics of included guidelines and consensus statements

Developer	Year	Country	Funding source	Target population	Target users	Guideline writers	Guideline review	Guideline update	Methods support	Evidence base
Europe										
NIV	2012	Netherlands	Government funding	Adults with hyponatremia	Clinicians, Internists	Multidisciplinary internists, epidemiologist	Dutch Association of Internists (NIV), expert peer review	In case of breakthrough changes in diagnosis or treatment	PROVA company specialized in Evidence Based Guideline Development	Systematic literature review
NHS	2011	UK	NS	Adults with hyponatremia in primary care	Primary care professionals within NHS	NS	NS	Planned in 2015	NS	Systematic literature review
GAIN*	2010	Northern Ireland	Government funding	Adults with hyponatremia	NS	Multidisciplinary anesthetists, clinical chemist, nephrologist	NS	3 years	NS	NS
AEEH*	2003-2004	Spain	NS	Patients with cirrhosis	NS	Gastroenterologists	NS	NS	NS	NS
EHN*	2013	Spain	NS	Hospitalized patients with SIADH	NS	Multidisciplinary endocrinologists, nephrologists, internists, hospital pharmacist	NS	NS	NS	Consensus statements
ERBP/ESE/ESICM	2014	Europe	Unrestricted grant from participating societies	Adults with hyponatremia	Health care professionals dealing with hyponatremia	Multidisciplinary nephrologists, endocrinologists, general internists, critical care physicians	External review by KHA-CARI, ESA, and members ERA-EDTA	5 years or earlier in case of new evidence requiring changes	ERBP methods support team	Systematic literature review
North America										
UF	2008-2009	USA	NS	Neurosurgery patients with hyponatremia	NS	Multidisciplinary neurosurgeons, nurse practitioners, nephrologists, critical care physician, endocrinologist, pharmacist, nurses	NS	NS	NS	Systematic literature review
HEP	2013	USA	Funding Unrestricted educational grant from pharmaceutical company	Patients with hyponatremia	NS	Endocrinologist, nephrologists	NS	NS	NS	Systematic literature review
Australia										
RCHM*	2012	Australia	NS	Children	NS	NS	External review within the hospital where appropriate	12 to 24 months	NS	NS

Table 1 Characteristics of included guidelines and consensus statements *(Continued)*

International										
EAH- ICD*	2007	USA, Canada, UK, Switzer-land, Canada, South Africa, New Zealand, Australia	No commercial sponsorship	People with exercise-associated hyponatremia	Medical personnel, athletes, greater public	Multidisciplinary endocrinologist, epidemiologist, nephrologists, emergency medicine physician, general practitioner, internist, sports physicians, exercise physiologists	NS	NS	NS	Systematic literature review

NIV, Nederlandse Internisten Vereniging [16]; NHS, National Health Service [17]; GAIN, Guidelines and Audit Implementation Network [22]; AEEH, La Asociacin Espaola para el Estudio del Hgado [23]; EHN, European Hyponatremia Network [25]; ERBP, European Renal Best Practice; ESE, European Society of Endocrinology; ESICM, European Society of Intensive Care Medicine [20]; UF, University of Florida [18]; HEP, Hyponatremia Expert Panel [19]; RCH Melbourne, the Royal Children s Hospital Melbourne [21]; EAH-ICD, International Exercise-Associated Hyponatremia Consensus Development Conference [24]; [Na], Serum sodium concentration; NS, Not stated; KHA-CARI, Kidney Health Australia, Caring for Australasians with Renal Impairment; ESA, Endocrine Society of Australia; ERA-EDTA, European Renal Association; European Dialysis and Transplant Association; *Classified as consensus statement.

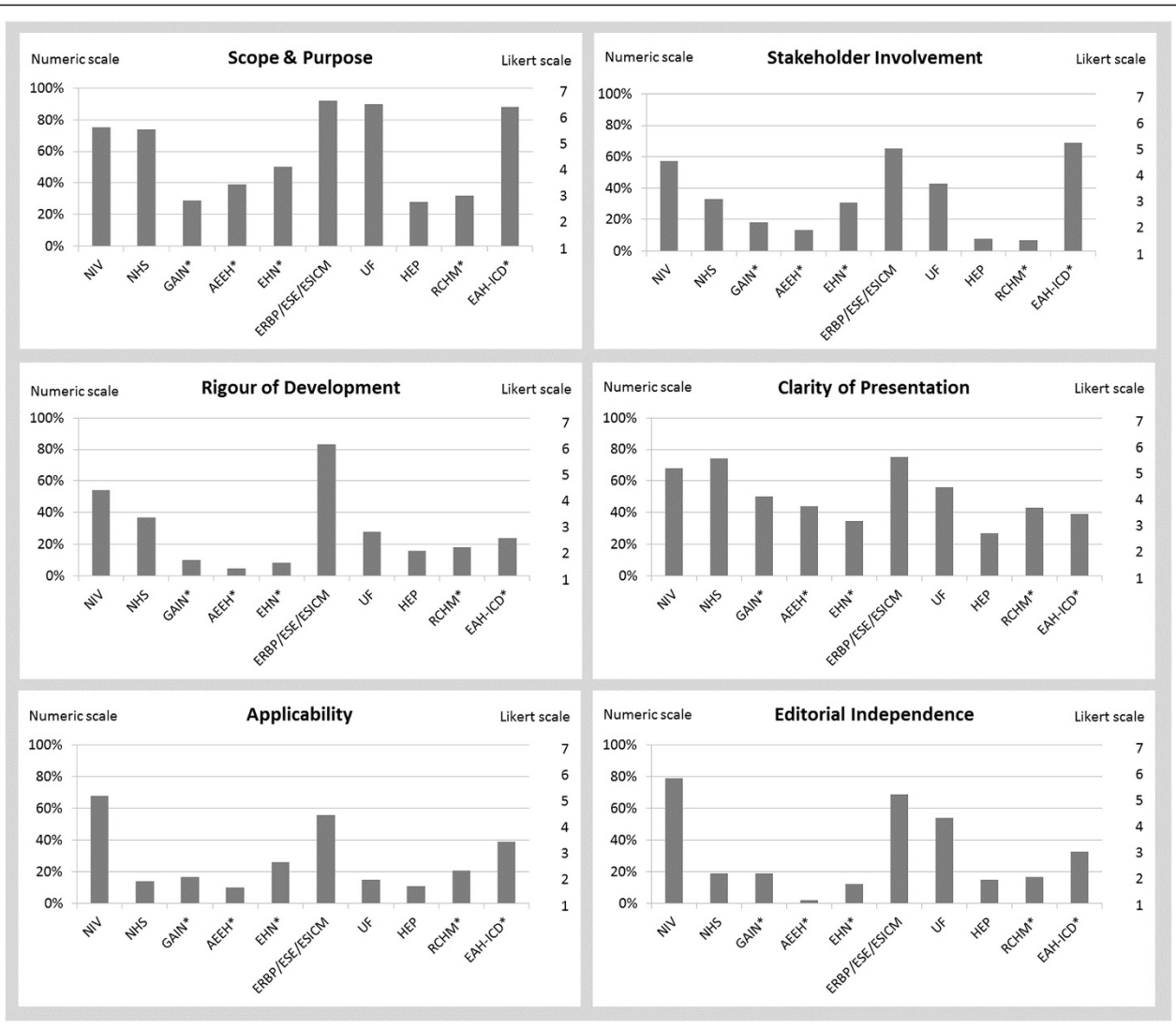

Figure 2 Guideline assessment according to the appraisal of guideline for research and evaluation (AGREE II) instrument. NIV, Nederlandse Internisten Vereniging [16]; NHS, National Health Service [17]; GAIN, Guidelines and Audit Implementation Network [22]; AEEH, La Asociacin Espa ola para el Estudio del Hgado [23]; ERBP, European Renal Best Practice; ESE, European Society of Endocrinology; ESICM, European Society of Intensive Care Medicine [20]; UF, University of Florida [18]; HEP, Hyponatremia Expert Panel [19]; RCH Melbourne, the Royal Children s Hospital Melbourne [21]; EAH-ICD, International Exercise-Associated Hyponatremia Consensus Development Conference [15]; *Classified as consensus statement. Note: items were originally scored on a Likert scale of 1 [Strongly Disagree] to 7 [Strongly Agree]. The numerical scores presented for each domain are a summary of individual item scores by each reviewer.

Synthesis of recommendations

The included guidance documents addressed three major themes: diagnosis, treatment, and speed of correction.

Approaches to diagnostic strategies for hyponatremia

Seven guidance documents covered diagnosis and differential diagnosis of hyponatremia [16-22]. Table 2 shows the key recommendations. The key areas addressed included the threshold for initiating diagnostic workup, confirmation and classification of hypotonic hyponatremia, and identification of the underlying disorder.

Guidance documents differed somewhat in their recommended threshold for starting diagnostic assessment. Six recommended starting diagnostic assessment when the serum sodium concentration dropped below 135 mmol/L [17,19-23] and to confirm hypotonicity through a measured serum or plasma osmolality <275 to 285 mOsm/kg [16-20,22]. Two others set lower thresholds of serum sodium concentration at <131 mmol/L [18] and <130 mmol/L [23]. Six guidance documents advised classifying hypotonic hyponatremia into categories of hypovolemia, euvolemia, and hypervolemia to aid differential diagnosis and guide treatment [16-22]. Most guidance documents recom-

Table 2 Summary of recommendations for approaches to diagnosis of hyponatremia by included guidance documents

	Guideline Organization/Society									
Criteria/Categories	NIV [16]	NHS [17]	GAIN [22]	AEEH [23]	EHN [25]	ERBP/ESE/ ESICM [20]	UF [18]	HEP [19]	RCHM [21]	EAH-ICD [24]
Threshold workup [Na]	<135 mmol/L	<135 mmol/L	<135 mmol/L	<130 mmol/L	<135 mmol/L	<135 mmol/L	<131 mmol/L	<135 mmol/L	<135 mmol/L	
Confirming hypotonic hyponatremia	Serum osmolality <275 mOsm/kg	Plasma osmolality <280 mOsm/kg	Serum osmolality <275 mOsm/kg		Plasma osmolality <275 mOsm/kg	Serum osmolality <275 mOsm/kg	Serum osmolality <285 mOsm/kg	Plasma osmolality <280 mOsm/kg	Serum osmolality threshold not stated	
How to classify hypotonic hyponatremia to aid identification of underlying cause										
Volume status/ hydration state/ extracellular fluid status	Clinical evaluation	Physical examination/clinical signs of dehydration or edema	Physical examination/clinical signs of dehydration or edema		Physical examination/ clinical signs of low circulating volume	Physical examination/ clinical signs of dehydration or edema	Physical examination/ laboratory measurements	Physical examination/ laboratory measurements	To assess but method not stated	
Urinary [Na]/Threshold	30 mmol/L	Spot urine: 20 30 mmol/L	15 mmol/L		40 mmol/L	30 mmol/L	25 mmol/L	Spot urine: 20 30 mmol/L	No threshold stated	
Urinary osmolality/ Threshold	100 mOsm/kg	100 mOsm/kg	100 mOsm/kg		100 mOsm/kg	100 mOsm/kg	100 mOsm/kg	100 mOsm/kg	No threshold stated	
How to identify the underlying disorder										
History		Medications	Medications			Diuretic use				
		Fluid intake	Recently prescribed intravenous fluids							
		Nocturnal polyuria	Vomiting/diarrhea							
Lab tests										
Serum potassium concentration	+	+							+	
Serum chloride concentration		+							+	
Serum urea concentration	+/	+					+/	+/	+	
Serum creatinine concentration	+	+					+/	+/	+	
Serum glucose concentration	+	+	+/			+			+	

Table 2 Summary of recommendations for approaches to diagnosis of hyponatremia by included guidance documents *(Continued)*

Urinary potassium concentration	+				+		
Renal tests			+				
Liver tests			+		+/		
Urinary protein		+/					
Thyroid function tests	+/	+/	+/		+/		
Adrenal function tests	+/	+/	+/		+/		
Serum protein electrophoresis		+/					
Urine protein electrophoresis		+/					
Fractional sodium excretion	+/						
Serum uric acid concentration	+/	+/			+	+/	
Fractional uric acid concentration	+/						
Fractional excretion urea	+/						
Urinary chloride concentration	+/				+	+/	
Molar weight urine	+/						
Serum bicarbonate concentration					+/		
Hematocrit					+/		

[Na], Serum sodium concentration; +, always; +/ , If clinically indicated/sometimes useful.
NIV, Nederlandse Internisten Vereniging [16]; NHS, National Health Service [17]; GAIN, Guidelines and Audit Implementation Network [22]; AEEH, La Asociacin Espaola para el Estudio del Hgado [23]; EHN, European Hyponatremia Network [25]; ERBP, European Renal Best Practice; ESE, European Society of Endocrinology; ESICM, European Society of Intensive Care Medicine [20]; UF, University of Florida [18]; HEP, Hyponatremia Expert Panel [19]; RCH Melbourne, the Royal Children s Hospital Melbourne [21]; EAH-ICD, International Exercise-Associated Hyponatremia Consensus Development Conference [24].

mended a clinical assessment of hydration status and a urinary sodium concentration as well as a urinary osmolality measurement, although specific criteria, thresholds, and algorithms differed.

Most guidance documents proposed additional laboratory tests that could be of value to identify the underlying disorder, but they varied substantially regarding which tests to use in what situation and which reference values to use. Only two explicitly recommended taking a history of drug intake and symptoms as part of the assessment [17,22]. Four presented an algorithm to guide differential diagnosis [16,18,20,22].

Approaches to treatment for hyponatremia

Table 3 shows the recommendations for the medical management of hyponatremia. Guidance documents distinguished treatment scenarios based on whether patients had severe symptoms [17-22,24,25] or whether the hyponatremia was acute (48 h) or chronic [16]. All but one discussed treatment in the setting of severe symptoms and recommended infusion of hypertonic saline, usually specified as having a concentration of 3% [17,19-21,24,25]. One suggested using a formula to guide the infusion speed of a continuous infusion [16], five others recommended giving a fixed dose [19,20,22,24,25], or a dose adjusted to body weight [21,25] with repeated serum sodium concentration measurements to check progression [16,20-22,25].

Patients without symptoms of hyponatremia were assumed to have chronic onset hyponatremia, and treatment suggestions were mostly dependent on the classification hypovolemic, euvolemic, or hypervolemic. Only three guidance documents specifically advised treating the underlying condition [19,22]. Seven suggested 0.9% saline in hypovolemia [16-22], with infusion speeds calculated with Adrogu-Madias [22], until restoration of blood pressure [17,19] or until nasogastric rehydration could start [21].

For euvolemic asymptomatic hyponatremia, the majority recommended fluid restriction as the first-line treatment [16-25]. Five guidance documents proposed a number of other interventions as second-line treatments including loop diuretics [16,18,20,25], demeclocycline [16-19], urea [16,19,20,25], vasopressin receptor antagonists [16,17,25], or lithium [18]. One guideline specifically recommended against vasopressin receptor antagonists in case of a serum sodium concentration <125 mmol/L [20].

For hypervolemic asymptomatic hyponatremia, seven guidance documents recommended fluid restriction as the first-line treatment [16,17,19-23] (Table 3). Three guidance documents advocated concomitant salt restriction, without clear dose recommendations [17,19,22], and one to avoid hypotonic infusion solution [21]. Three additionally proposed loop diuretics [16,17,19] and three others generally stated to treat the underlying disease [17,20,22], whereas one advised to consider stopping diuretics [23]. One guideline additionally proposed demeclocycline and two proposed vasopressin receptor antagonists as a second-line treatment for refractory hyponatremia [17,19], whereas one guideline specifically recommended against both demeclocycline and vasopressin receptor antagonists [20].

Targets and limits of speed of correction

Table 4 shows the key recommendations. The key areas include targets and limits for increase in serum sodium concentration.

Seven guidance documents provided targets or aims for the increase in serum sodium concentration in case of symptomatic and/or acute hyponatremia [16,17,19-22,25]. Seven guidance documents provided limits for the increase in serum sodium concentration that should not be surpassed [16-22,25]. Five did so independent of symptoms [16,18,20,22,25]. Limits usually varied between 8 to 12 mmol/L during the first 24 hours [16-22,25] and 18 mmol/L during the first 48 hours [16,17,19,20,25], irrespective of whether hyponatremia was acute or chronic [16,17,20,25]. Three guidance documents set a stricter limit of <8 mmol/L during the first 24 hours in cases where the patient was believed to be high risk for developing osmotic demyelination syndrome [16,19,25]. Four discussed what to do in case of overcorrection, i.e., to stop current treatment and to consider re-lowering serum sodium concentration by starting hypotonic infusion and administering 1 to 4 μg desmopressin every 6 to 8 hours [16,19,20,25].

Discussion

We found five clinical practice guidelines and five consensus statements covering the diagnostic approach to and treatment of hyponatremia. Although most used serum osmolality, volume status, urinary sodium, and urinary osmolality to guide differential diagnosis, they differed in classification thresholds, what additional tests to consider, and when to initiate diagnostic work-up. Most advocated hypertonic NaCl in severely symptomatic, acute onset hyponatremia and NaCl 0.9%, fluid restriction, and cause-specific therapy for hypovolemic, euvolemic, and hypervolemic hyponatremia, respectively. However, they somewhat differed in the limits for speed of increase in serum sodium concentration and which specific medications to use. The reasons for offering different recommendations are undoubtedly multifactorial. They may in part be explained by the fact that recommendations were issued by organizations differing in context and scope. It is also very likely that some variability in guidance arose through limitations in the evidence available for guideline developers to base their recommendations on [8]. In the most recent guideline on diagnosis and treatment of hyponatremia, 98% of the

Table 3 Summary of recommendations for approaches to treatments for hyponatremia by included guidance documents

	Guideline Organization/Societies									
Criteria/ categories	NIV [16]	NHS [17]	GAIN [22]	AEEH [23]	EHN [25]	ERBP/ESE/ ESICM [20]	UF [18]	HEP [19]	RCHM [21]	EAH-ICD [24]
Symptoms										
Acute Onset (<48 h)	NaCl >1% Infusion speed may be guided by Adrogu-Madias	NaCl 3%	NaCl 2.7% 200 mL over 30 min		NaCl 3% 100 mL/ 10 min up to 3 or infused at 0.5 2 mL/kg/h	NaCl 3% 150 mL/ 20 min up to 4	NaCl >1%	NaCl 3% 100 mL/ 10 min up to 3 or infused at 0.5 2 mL/kg/h	NaCl 3% 4 mL/kg over 30 min	NaCl 3% 100 mL bolus
Hypovolemia								NaCl 0.9% until blood pressure restored		
Euvolemia			Fluid restriction							No hypotonic fluids
			Stop offending drugs							
			Stop hypotonic fluids							
Hypervolemia			Furosemide					Furosemide		
Chronic onset (>48 h)	NaCl >1% Infusion speed calculation may be guided by Adrogu-Madias	NaCl 3%	Only if severe symptoms NaCl 2.7% 200 mL over 30 min infusion speed by may be guided Adrogu-Madias		NaCl 3% 100 mL/ 10 min up to 3 or infused at 0.5 2 mL/kg/h	NaCl 3% 150 mL/ 20 min up to 4	NaCl >1%	NaCl 3% 100 mL/ 10 min up to 3 or infused at 0.5-2 mL/kg/h		
Hypovolemia			NaCl 0.9% 1 L over 2 4 h infusion speed may be guided by Adrogu-Madias					NaCl 0.9% until blood pressure restored		
Euvolemia			Fluid restriction							
			Stop offending medications							
			Stop hypotonic fluids							
Hypervolemia			Fluid restriction					Furosemide		
			Salt restriction							
No symptoms										
Acute onset (<48 h)	NaCl >1% Infusion speed by Adrogu-Madias		Treat underlying condition			Stop offending fluids and medications, treat underlying		Treat underlying condition		

Table 3 Summary of recommendations for approaches to treatments for hyponatremia by included guidance documents *(Continued)*

						condition NaCl 3% 150 mL/20 min			
Chronic onset (>48 h)	Treat underlying condition		Treat underlying condition			Stop non-essential fluids Stop offending medications Treat underlying condition		Treat underlying condition	
Hypovolemia	NaCl 0.9%	NaCl 0.9% until blood pressure restored	NaCl 0.9% infusion speed may be guided by Adrogu-Madias			NaCl 0.9% or balanced crystalloid 0.5 1 mL/kg/h	NaCl 0.9%	NaCl 0.9% until blood pressure restored	Nasogastric rehydration
	NaCl tablets							No VPA	NaCl 0.9%
Euvolemia	Fluid restriction, dose dependent on serum and urinary electrolytes	Fluid restriction, 500 1,000 mL/d	Fluid restriction		Fluid restriction <500 1,000 mL/d	Fluid restriction	Fluid restriction	Fluid restriction 500 mL below average daily urine output	Fluid restriction, no hypotonic fluids
		No salt restriction	Salt restriction		Salt 5 8 g/d			No salt restriction	
	Loop diuretics				Furosemide 20 60 mg/d + oral NaCl	Loop diuretics, low dose + oral NaCl	Diuretics		
	Demeclocycline	Demeclocycline				No demeclocycline	Demeclocycline	Demeclocycline, 600 1,200 mg/d	
	Urea				Urea 30 g/d	Urea, 0.25 0.5 g/kg/d	Urea	Urea, 15 60 g/d	
	Vasopressin receptor antagonist	Vasopressin receptor antagonist			Tolvaptan 15 60 mg/d	No vasopressin receptor antagonists			
Hypervolemia		Treat underlying condition							
	Fluid restriction, dose dependent on serum and urinary electrolytes	Fluid restriction	Fluid restriction	Fluid restriction <1,000 mL/d		Fluid restriction		Fluid restriction, <insensible losses + urine output	Fluid restriction
	Loop diuretics	Salt restriction	Salt restriction	No NaCl >0.9%				Salt restriction	
		Demeclocycline		Stop diuretics		No demeclocycline		Possibly vasopressin receptor antagonist	
		Vasopressin receptor antagonist				No vasopressin receptor antagonist			

NIV, Nederlandse Internisten Vereniging [16]; NHS, National Health Service [17]; GAIN, Guidelines and Audit Implementation Network [22]; AEEH, La Asociacin Espaola para el Estudio del Hgado [23]; EHN, European Hyponatremia Network [25]; ERBP, European Renal Best Practice; ESE, European Society of Endocrinology; ESICM, European Society of Intensive Care Medicine [20]; UF, University of Florida [18]; HEP, Hyponatremia Expert Panel [19]; RCH Melbourne, the Royal Children s Hospital Melbourne [21]; EAH-ICD, International Exercise-Associated Hyponatremia Consensus Development Conference [24].

Table 4 Summary of recommendations for targets and limits for speed of correction of hyponatremia by included guidance documents

	Guideline Organization/Societies									
Criteria/ categories	NIV	NHS	GAIN	AEEH	EHN	ERBP/ESE/ESICM	UF	HEP	RCHM	EAH-ICD
	[16]	[17]	[22]	[23]	[25]	[20]	[18]	[19]	[21]	[24]
Targets [Na] increase										
Symptoms	Independent of symptoms	If symptoms	If symptoms		If symptoms	If symptoms		If symptoms	Until seizures resolve or [Na] >125 mmol/L	
Acute onset (<48 h)	1 2 mmol/L/h initially	Until [Na] >120 mmol/L independent of onset	1 2 mmol/L/h first 2 3 h		1 6 mmol/L first 2 h	5 mmol/L first h		4 6 mmol/L urgently	Independent of onset	
Chronic onset (>48 h)			0.5 1 mmol/ L/h first 2 3 h		1 6 mmol/L first 2 h	5 mmol/L first h		If seizures or coma 4 6 mmol/L urgently, otherwise 4 6 mmol/L per 24 h		
Limits [Na] increase										
Symptoms	Independent of symptoms	If no symptoms	Independent of symptoms		Independent of symptoms	Independent of symptoms	Independent of symptoms	If no symptoms	Symptom dependent	
Acute onset (<48 h)	If no risk of ODS ≤10 mmol/L per 24 h ≤18 mmol/L per 48 h If risk of ODS <8 mmol/L per 24 h	≤8 12 mmol/L per 24 h ≤18 mmol/L per 48 h	<12 mmol/L per 24 h		If no risk of ODS ≤10 mmol/L per 24 h ≤18 mmol/L per 48 h If risk of ODS <8 mmol/L per 24 h	≤10 mmol/L first 24 h ≤8 mmol/L every 24 h thereafter	≤10 mmol/L per 24 h	No limits	≤8 mmol/L per 24 h after seizures resolve, Independent of onset	
Chronic onset (>48 h)	<8 mmol/L per 24 h	≤8 12 mmol/L per 24 h ≤18 mmol/L per 48 h	<12 mmol/L per 24 h		<8 12 mmol/L per 24 h <18 mmol/L per 48 h	≤10 mmol/L first 24 h ≤8 mmol/L every 24 h thereafter	≤10 mmol/L per 24 h	<8 12 mmol/L per 24 h <18 mmol/L per 48 h		

[Na] Serum sodium concentration.
NIV, Nederlandse Internisten Vereniging [16]; NHS, National Health Service [17]; GAIN, Guidelines and Audit Implementation Network [22]; AEEH, La Asociacin Espaola para el Estudio del Hgado [23]; EHN, European Hyponatremia Network [25]; ERBP, European Renal Best Practice; ESE, European Society of Endocrinology; ESICM, European Society of Intensive Care Medicine [20]; UF, University of Florida [18]; HEP, Hyponatremia Expert Panel [19]; RCH Melbourne, the Royal Children s Hospital Melbourne [21]; EAH-ICD, International Exercise-Associated Hyponatremia Consensus Development Conference [24].

graded recommendations were based on very low and low level of evidence, while none were based on a high level of evidence. The lack of high quality evidence may have increased the part opinion had to play in framing the recommendations. In addition, the evidence that was available may have been interpreted differently dependent on the importance for decision making given to certain outcomes (e.g., serum sodium concentration). Finally, differences in personal experience due to differing availability of medications may partly explain possible differences in perception of uncertainties around drug safety.

However, it is also possible that discrepancies between guidance documents may in part be explained by differences in underlying methods of development. Quality, as assessed by AGREE II, was suboptimal at best, with only two documents obtaining a score >50% for each of the six quality domains [16,20]. The findings suggest that several aspects related to methodological rigor of development, stakeholder involvement, applicability, and editorial independence could be improved, possibly improving consistency in provided guidance. This is in line with the findings of a recent overview of 42 appraisal studies including a total of 626 clinical practice guidelines across several clinical disciplines [26]. For guidelines to be trustworthy, they must be i) founded on high quality systematic reviews, ii) include the relevant stakeholders, and iii) be applicable in clinical practice [9].

Only half of the guidance groups stated they had conducted a systematic review of the evidence. Save one, the reviews would not have met the Institute of Medicine s criteria for reporting high-quality systematic reviews [20,27], because key methods for finding and assessing individual studies as well as synthesizing the body of evidence were not described. Conducting high-quality systematic reviews requires specific methodological expertise and support which may not be available to most groups [27]. One solution might be to harmonize effort across organizations, thus focusing resources, allowing higher quality reviews and reducing duplication and possibly inconsistency between guidelines.

Six groups included healthcare professionals from different specialties [16,18,20,22,24,25]. Multidisciplinary contribution serves to broaden the approach to health-care problems, increase the completeness of evidence-finding strategies, and help to identify hurdles to implementation. When reflecting on approaches to hyponatremia, bringing together several disciplines mirrors the clinical reality of multiple specialty areas dealing with the same problem but looking at it from a different angle. Only one of the development groups reported considering patients views and experiences, but even then did so to a limited extent [20]. Decisions on clinical care should factor in patient values and preferences. Interventions for chronic hyponatremia, such as fluid restriction, may affect quality of life and patient preference should influence the ultimate recommendations.

Low scores for applicability mostly reflect the absence of describing barriers to guideline implementation and failure to provide tools for putting the recommendations into practice. In part, guidelines are designed to deal with the challenges of increasing knowledge and time-pressure. They are designed to help make decisions at the point of care. However, being often lengthy publications without layered presentation of information, it is likely that the majority of the guidance documents may not reach their target audience or stimulate implementation. Four guidance documents provided algorithms for diagnosis or treatment [16,18,20,25]; although these are likely to increase the utility of a guideline, it is unclear to what extent they truly improve implementation of the recommendations. How to best communicate evidence-based recommendations to the relevant stakeholders is a recent but active area of research lead by the DECIDE consortium [28]. With results of their research expected, guideline developers will have additional targets for improving the applicability in the future.

To our knowledge, this is the first attempt to systematically synthesize and appraise clinical guidelines on the diagnosis and treatment of hyponatremia In accordance with the Prisma statement, we conducted a comprehensive literature search and searched an additional 337 websites of specialist societies and guideline organizations [29] (Additional file 6). We used AGREE II, a validated and reliable instrument, and an adequate number of reviewers to individually appraise the guidance documents [30]. On top of the individual appraisals, we included an attempt to resolve major discrepancies and increase consistency by introducing an audiotaped group consensus meeting. During this meeting, reviewers could explain and motivate their scores and adapt them if they wanted to. This mostly resulted only in modest downgrading of domain scores by 1% to 10%. Most of the changes happened because reviewers felt they had scored inconsistently for a same rationale, or because they missed information during the initial appraisal that was in fact available in the document. Although the scores did not change substantially, the group felt the discussion further highlighted the qualitative differences between the guidance documents. In addition, even the reviewers with large deviations from the mean in their initial scores felt they agreed with the conclusion. It means that final average scores were truly a product of consensus rather than a mathematical calculation, as proposed in the original AGREE protocol. We believe that a consensus meeting is valuable in any guideline appraisal process, and particularly useful if reviewer groups have the intention to select a guideline for local use.

This study has its limitations. We based our assessment on what guideline organizations actually reported. Reporting by guideline developers may not wholly reflect what occurred in practice with respect to the AGREE criteria, and we did not seek additional clarification. However, contacting guideline developers is not standard practice when using AGREE as the instrument specifically aims to provide a framework for assessing the quality of reporting of recommendations. We aimed to summarize the existing recommendations on diagnosis and treatment of hyponatremia as formulated by other guideline development groups and to evaluate the quality of the guideline development process. We did not aim to summarize or critically appraise the evidence base itself. Consequently, it is difficult to assess to what extent differences between guidance documents stem from differences in development procedures rather than important limitations in the evidence base that underpin individual recommendations. Secondly, the purpose of using the AGREE instrument was not to accuse guideline development groups of being biased, but rather to highlight both strengths and weaknesses of existing guidance to suggest on how we could make improvements in the future.

Calculation of summary scores for each domain across reviewers required summing up all the scores of the individual items in a domain for each reviewer and then standardizing this total as a percentage of the maximum possible score for that domain. In doing so, the originally semi-qualitative Likert scale was converted to a quantitative score. This may have introduced numeric differences between the guidance documents that were beyond the discriminatory ability of the tool and possibly negligible in practice. Finally, we acknowledge that four of the authors of this paper also authored one of the guidelines included in this review. Although we aimed to judge all guidance documents fairly against the criteria outlined by the AGREE instrument, we cannot rule out that a subconscious intellectual competing interest unduly influenced the scoring.

Conclusions

Current guidelines on the assessment and treatment of hyponatremia often fail to meet methodological criteria for development and reporting as described by AGREE II. Despite many similarities, recommendations are sometimes inconsistent, but to what extent this is attributable to the underlying development process remains unclear.

Additional files

Additional file 1: Table S1. Search strategies.

Additional file 2: Table S2. Data extraction template.

Additional file 3: Table S3. Structure and content of the AGREE instrument.

Additional file 4: Table S4. Table of excluded studies.

Additional file 5: Table S5. Mean scores across reviewers for the individual AGREE II domain items.

Additional file 6: PRISMA checklist.

Abbreviation

AGREE II: Appraisal of guidelines for research and evaluation II.

Competing interests

Evi Nagler is a member of the Methods Support Team of European Renal Best Practice (ERBP). She is also one of the authors of the Clinical Practice Guideline on the diagnosis and treatment of hyponatremia, developed in a joint venture with the European Society of Endocrinology and the European Society of Intensive Care Medicine and one of the guidelines included in the current review. Jill Vanmassenhove has no relevant disclosures. Sabine van der Veer is a member of the Methods Support Team of European Renal Best Practice (ERBP). She is also one of the authors of the Clinical Practice Guideline on the diagnosis and treatment of hyponatremia, developed in a joint venture with the European Society of Endocrinology and the European Society of Intensive Care Medicine and one of the guidelines included in the current review. Ionut Nistor is a member of the Methods Support Team of ERBP. Wim Van Biesen is the Chair of ERBP, he is also one of the authors of the Clinical Practice Guideline on the diagnosis and treatment of hyponatremia, developed in a joint venture with the European Society of Endocrinology and the European Society of Intensive Care Medicine and one of the guidelines included in the current review. Angela Webster has no relevant disclosures. Raymond Vanholder is member of ERBP, he is also one of the authors of the Clinical Practice Guideline on the diagnosis and treatment of hyponatremia, developed in a joint venture with the European Society of Endocrinology and the European Society of Intensive Care Medicine and one of the guidelines included in the current review.

Authors contributions

EN designed and conducted the systematic review, conducted the systematic search, selected and critically appraised the studies, collected the data, and wrote and revised the manuscript. JV selected and critically appraised the studies, collected the data, and revised the manuscript. SVDV critically appraised the studies. IN conducted the systematic search and critically appraised the studies. WVB designed the systematic review, critically appraised the studies, and wrote and revised the manuscript. AW designed the systematic review and wrote and revised the manuscript. RV designed the systematic review and wrote and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Evi Nagler, Sabine van der Veer, and Ionut Nistor are fellows of the Methods Support Team of European Renal Best Practice (ERBP), supported by a grant of the European Renal Association- European Dialysis Transplantation Association (ERA-EDTA).

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Received: 20 April 2014 Accepted: 7 November 2014
Published online: 11 December 2014

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doi:10.1186/s12916-014-0231-1
Cite this article as: Nagler *et al.*: Diagnosis and treatment of hyponatremia: a systematic review of clinical practice guidelines and consensus statements. *BMC Medicine* 2014 **12**:231.

DOI: 10.7860/JCDR/2019/39957.12554

Original Article

Internal Medicine Section

Hyponatremia in Elderly In-Patients

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ABSTRACT

Introduction: Hyponatremia, the most common dyselectrolytemia, frequently occurs in elderly patients. Multiple aetiologies, association of comorbids play a major role in hyponatremia of elderly patients. Prolonged hospital stay and increased mortality are the consequences.

Aim: To study the prevalence, common aetiologies, comorbids and clinical outcomes of hyponatremia in elderly in-patients.

Materials and Methods: A prospective, observational study was conducted in a teaching hospital on 950 adults ≥60 years of age, admitted to the Post-graduate Department of Medicine, over a period of 12 months. Detailed history, clinical examination, outcomes, laboratory investigations, imaging studies, diagnoses and causes were recorded. For statistical analyses, histogram, Kolmogrove test for normality test and then Independent t-test, Wilcoxon rank sum test, Pearson's chi-square test, Fisher's-exact tests were used.

Results: After excluding 32 patients of pseudo and hyper-natremia, 440 patients (47.9%) had hyponatremia (s. Na^+ level of <135 mEq/L) and 478 patients (52.0%) had normal sodium (135-145 mEq/L). The mean age of hyponatremic patients was 69.87±7.94 and 70±8.18 in normonatremic patients (p=0.815). The mean Na^+ level was 122.08±8.68 mEq/L in hyponatremic patients and 138.05±2.71 in normonatremic patients. Hypovolemic hyponatremia was most frequent (42.0%). The leading aetiologies were diuretics (28.8%), acute renal failure (27.9%), and severe sepsis (15.2%) but 61.8% of patients with hyponatremia had multiple factors. Hypertension was the most common comorbid (63%) and presence of multiple comorbid was significantly associated with hyponatremia (p<0.001). Hyponatremic group, though hospitalised for longer period (p<0.001), higher mortality rate could not be established (p=0.699); not also with the severity of hyponatremia (p=0.06).

Conclusion: Elderly patients are highly predisposed to hyponatremia and are often dehydrated. Presence of multiple comorbid is a risk factor. Hyponatremia prolongs the hospital stay but severity of underlying illnesses may rather accelerate the mortality rate.

Keywords: Comorbid, Dehydration, Elderly, Sodium

INTRODUCTION

Hyponatremia, a very common electrolyte disorder in clinical medicine, most frequently occurs in elderly in-patients [1-3]. It is defined as s. Na^+ level of <135 mEq/L and observed to be occurring in 15-30% of hospitalised patients. However, in elderly patients, the prevalence rate has been reported to be even higher up to 50% [3-5].

Ageing results in impairment of water-excretory capacity due to decreased GFR, reduction in total body water content, higher sensitivity to osmotic stimuli, and associated with multiple comorbidities and exposure to multiple drugs [6-10]. Besides, low salt diet followed by many elderly patients and hypoproteinemia due to background illness or malnutrition may also contribute to hyponatremia in this age group [11]. Therefore, ageing itself is considered a significant risk factor for hyponatremia.

Hyponatremia can be of three types-hypertonic hyponatremia, isotonic hyponatremia or hypotonic hyponatremia. Hypotonic hyponatremia is the most common type encountered in clinical practice and further categorised in three-ways based on patient's volume status- hypervolemic, euvolemic and hypovolemic. Hyponatremia, resulting from hyperlipidemia, paraproteinemia is pseudohyponatremia [12].

Clinical manifestations of hyponatremia count on multiple factors like the duration of the development of symptoms, severity of the decline in sodium level and the patient's overall health [13]. Mild hyponatremia usually remains asymptomatic and GI manifestations occur with s. Na^+ ~ 125 mEq/L. As the s. Na^+level fall further CNS symptoms such as confusion, lethargy, focal neurologic deficits, disorientation and agitation usually manifest. Severe neurologic features such as seizure and coma are usually seen when the sodium level falls acutely (<48 hours) below 115 mEq/L [12].

Mild chronic hyponatremia can cause gait impairment, attention deficit, increased risk of falls and osteoporosis [14,15]. Patients with chronic hyponatremia usually develop neurologic symptoms when sodium level falls below 110 mEq/L due to acute exacerbation [16].

Despite being a treatable condition, hyponatremia is associated with prolonged hospital stay and increased mortality rate [10,17].

The present study aimed to determine the prevalence, common aetiologies, comorbids and clinical outcomes of hospitalised hyponatremic elderly patients.

MATERIALS AND METHODS

A prospective, observational study was carried out over a 12 month period from August 2017 to July 2018 in a teaching hospital. Ethical Committee approval and informed consents were taken prior to the study. All patients of 60 years and above, admitted to the Post-graduate Department of Medicine were included in the study and 950 elderly patients admitted during the period were studied. Detailed history and thorough clinical examination were done. Clinical data including demographics, presenting symptoms, comorbid, drug history, clinical examination findings, volemic status, laboratory investigations, treatment and final outcome were recorded. Patients with pseudohyponatremia and hypernatremia were excluded.

Investigations included complete haemogram, renal function test with serum uric acid, liver function test, blood glucose, routine urine examination, electrolytes, lipid profile, thyroid function test, morning serum cortisol. Imaging studies (chest radiograph, ultrasonography of abdomen and pelvis, CT Scan of brain), ECG, echocardiogram were done in patients when indicated clinically to detect further comorbid conditions and aetiologic factors. Serum sodium and urine sodium were measured by ion sensitive electrode method.

Serum osmolality and urine osmolality were measured by freesing point depression osmometer. Hyponatremia was defined in patients having serum Na^+ level of <135 mEq/L. The hyponatremic patients were further classified into hypo-, hyper-and eu-volemic groups based on the clinical findings of their volemic status. Multifactor aetiology was defined when more than one factor, known to cause hyponatremia were present simultaneously in a patient. Severe sepsis was defined as confirmed or suspected infection with hypofunction of distant organ [18] and Syndrome of Inappropriate Anti Diuretic Hormone (SIADH) was diagnosed by 'Bartter and Schwartz criteria' [19].

STATISTICAL ANALYSIS

All the data were analysed by using statistical package SPSS, version 20.0. Data were first analysed for normal distribution by Kolmogorov-Simrinov, Q-Q Plot, Histogram and then Independent t-test, Wilcoxon rank sum (Mann-Whitney U) test, Pearson's chi-squared test and Fisher-exact test were used as applicable, to compare the variables. The p-value of <0.05 was of statistical significance.

RESULTS

Out of total 950 elderly patients studied, 32 patients (six patients of hypertriglyceridemia, one multiple myeloma, 11 patients with hypernatremia and 14 patients with hyperglycaemia) were excluded. Of the remainder 918 patients, 478 (52.1%) patients had normal serum sodium level (135-145 mEq/L). The mean age of the patients was 69.87±7.94 and 70.0±8.18 in hyponatremic and normonatremic patients, respectively (p=0.815). Females constituted 44.8% in hyponatremic and 45.2% in normonatremic patients group. The baseline parameters of patients in the study groups are described in [Table/Fig-1] and no significant difference was found between the groups, regarding age, sex and BMI.

Parameters	Hyponatremic elderly patients	Normonatremic elderly patients	p-value
No. of Patients	N=440	N=478	
Sex: Female (% of total)	197 (44.8%)	216 (45.2%)	0.899[#]
Age (years) Mean±SD	69.87 (±7.946)	70.00 (±8.182)	0.815[@]
BMI Mean (±SD)	22.517 (±4.309)	22.198 (±4.624)	0.50[@]
(Min-Max)	(12.82-38.93)	(11.69-37.31)	
Comorbid			
No. of Comorbid Mean (±SD)	1.46 (±0.92)	1.04 (±0.90)	<0.001[##]
Absence of Comorbid N (%)	60 (13.6%)	148 (31.0%)	<0.001[#] {OR: 0.352; 95% CI 0.252-0.492}
Presence of multiple (≥2) Comorbid	202 (45.9%)	137 (28.7%)	<0.001[$] {OR : 2.113; 95% CI 1.608-2.775}
Na+level on admission			
Mean (±SD)	122.08 (±8.68)	138.05 (±2.713)	<0.001[&]
(Min-Max)	(94-134)	(135-145)	
Length of Hospital Stay			
Median days	6	5	<0.001[&]
Mean (±SD)	7.53 (±6.109)	5.66 (±3.645)	
Death N (%)	20 (4.5%)	19 (4.0%)	0.669[$$]

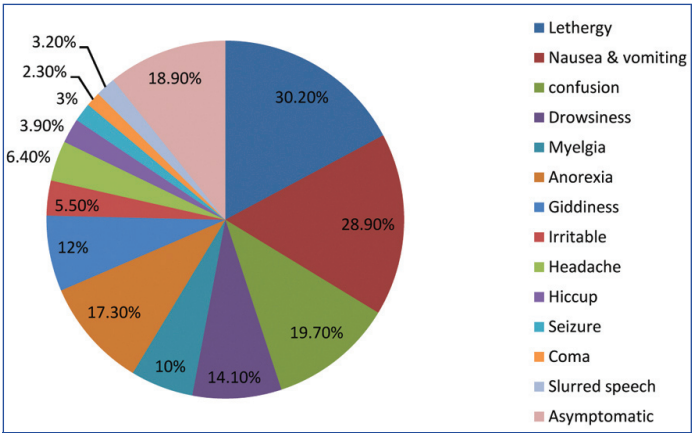
[Table/Fig-1]: Baseline parameters and comparison of proportions across the study groups.
Min: Minimum; Max: Maximum; SD: Standard deviation; CI: Confidence interval; OR: Odd ratio [#]Pearson Chi-Square test; [@]Independent 't' test; [##]Mann whitney u-test; [$]Pearson (Mantel-Haenszel test); [&]Wilcoxon ranksum test; [$$]Pearson test

Hyponatremia was found in 46.3% of all hospitalised elderly medicine patients, including patients who developed hyponatremia during hospital stay (N=39). The mean sodium level was 122.08±8.68 mEq/L in hyponatremic patients and 138.05±2.71 in normonatremic group (p<0.001). Hypovolemic hyponatremia was most common (42.0%, N=185); followed by hypervolemic (32.5%, N=143) and euvolemic (25.5%, N=112) and 53 patients (12.0%) had satisfied the diagnostic criteria for SIADH. Most of the hyponatremia in the present study, was of multifactorial aetiology (61.8%, N=272). Use of diuretics (28.8%, N=127), acute renal failure (27.9%,N=123), GI loss (15.5%, N=68) were other leading causes. Among the diuretic users, 93 patients (21.1%) were using thiazides and 33 patients (7.5%), loop diuretics. A total of 139 patients had infections out of which 67 (15.2%) patients had severe sepsis. Other aetiologies are described in [Table/Fig-2]. Salt- restricted diet was followed by 47 (10.7%) patients and nutritional hypoalbuminemia (after excluding the underlying diseases causing protein loss) was found in 54 (12.3%) patients with hyponatremia.

Aetiologies	No. of patients% (N)
Multifactor	61.8 (272)
Diuretics	28.8 (127)
Acute Renal Failure	27.9 (123)
GI Loss	15.5 (68)
Severe sepsis	15.2 (67)
SIADH	12 (53)
CHF	7.7 (34)
CLD	5.9 (26)
CVA	7.4) (33)
LRTI	8 (35)
SAH	0.7 (3)
Hypothyroid	2.7 (12)
Adrenal insufficiency	0.9 (4)
Low salt intake	10.7 (47)
Hypoalbuminemia (Nutritional)	12.3 (54)

[Table/Fig-2]: Aetiological factors causing hyponatremia in the elderly patients (N=440).
GI: Gastrointestinal; SIADH: Syndrome of inappropriate anti diuretic hormone; SAH: Subarachnoid haemorrhage; LRTI: Lower respiratory tract infection; CHF: Congestive heart failure; CLD: Chronic liver disease; CVA: Cerebro-vascula accident

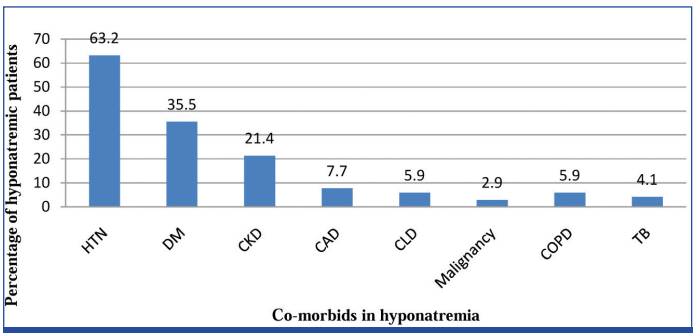
The most common mode of presentation was lethargy (30.2%). Other manifestations included nausea and vomiting (28.9%), confusion (19.7%), drowsiness and impaired consciousness (14.1%). Seizure and coma occurred in 3.0% (N=13) and 2.3% (N=10) of patients, respectively. 13 (3%) patients had fall and fractures in recent past (<6 month). 83 (18.9%) patients had no presenting symptoms attributed to hyponatremia [Table/Fig-3].



[Table/Fig-3]: Clinical manifestations of hyponatremia patients (N=440).

Hypertension was the most common comorbid condition detected (63.2%), followed by Diabetes mellitus (35.5%) and Chronic kidney disease (21.4%) in hyponatremic group. Other comorbid are depicted in [Table/Fig-4]. Absence of comorbid conditions was significantly present in 148 patients (31.0%) in normal serum sodium group of patients (p<0.001). Again, presence of

multiple (≥2) comorbid conditions was significantly associated with hyponatremia in elderly patients (p<0.001, OR 2.113; 95% CI 1.608-2.775) [Table/Fig-1].



[Table/Fig-4]: Co-morbids associated with hyponatremia study group.
DM: Diabetes mellitus; HTN: Hypertension; CAD: Coronary artery disease; CKD: Chronic kidney disease; CLD: Chronic liver disease; COPD: Chronic obstructive pulmonary disease; TB: Tuberculosis

Excluding the hospital stay in patients discharged against medical advice (N=21 in hyponatremia, N=15 in normonatremia), hyponatremic group had longer hospital stay, mean of 7.5±6.1 days as compared to mean of 5.6±3.6 days in normonatremic group; (median 6 days vs. 5 days) (p<0.001). Regarding outcome of the patients, 20 patients (4.5%) in hyponatremic group and 19 patients (4.0%) in control group died during hospitalisations; bearing no significant difference in mortality rate across the elderly groups (p=0.669). The mortality rate, among mild (s. Na^+ level of 126-134 mEq/L), moderate (116-125 mEq/L) and severe hyponatremia (≤115 mEq/L) were 2.7% (N=5), 8.0% (N=12) and 2.8% (N=3), respectively (Fisher's-exact test, p=0.06). Female (3.5%) versus male (5.3%) had died in hyponatremic group; whereas in control group, female 4.1% vs. male 3.8%.

DISCUSSION

The prevalence of hyponatremia in this study was 46.3% of all elderly medicine in-patients. Miller M et al., study revealed 53% of elderly in-patients aged 60 years and above, had hyponatremia over 12 months [20]. Other studies also observed the prevalence of hyponatremia in almost 50% of geriatric admissions [4,5]. In one Asian study, Siregar P, described the prevalence ratio of 2.79 for elderly compared to young group in hospitalised patients [21].

The slight male preponderance in this study is consistent with other recent studies of hyponatremia in elderly [22,23]. Similar to the study by Gill G et al., our study also had no sex difference between the two groups [24].

Hypovolemic hyponatremia was predominantly observed (42%). Cumming K et al., as well found 69.7% of hyponatremia due to dehydration and apprehended it could be 'frequently overlooked and underdiagnosed' [25]. In elderly, dehydration can be due to various factors including decreased body water content, less fluid intake, injudicious use of diuretics, predisposition to infections or a combination. Currently, there is no biological marker to detect volemic status and solely depends on clinical examination which is a drawback for accuracy in diagnosis, especially in older people [26].

Many previous studies, reported multifactorial aetiology as the most common cause of hyponatremia in elderly (51.3%, 75.3%, 72.7%) [7,25,27]. The present study, equate their findings by observing 61.8% of patients having multifactor in hyponatremic group. The other leading cause of hyponatremia in the present study was diuretics; of which the most frequent association being thiazides (21.5%). Liamis G et al., depicted thiazide as one of the commonest cause of hyponatremia in elderly [11]. Hypertension being the most frequent comorbid associated with elderly and widespread prescription of thiazide make the thiazide induced hyponatremia described as a 'silent epidemic'[28]. Euvolemic hyponatremia was found in 25.5% of patients and SIADH was diagnosed in 12% of cases in the present study reflecting it, as not a leading cause of hyponatremia in the elderly patients. Soiza RL et al., in their study, also pointed out the possibility of SIADH being over diagnosed in previous studies, especially in dehydrated elderly people [26].

Comorbid conditions are commonly present with the geriatric population and associated with hyponatremia in elderly patients. Mohan et al, in their study found 73% of hyponatremic patients had comorbid [29]. Similarly, in the present study 86.4% of patients in hyponatremic group had comorbid as compared to 69% in normonatremic group which is statistically significant (p<0.001). Moreover, the present study also observed the presence of multiple comorbid condition as a significant risk factor for development of hyponatremia in elderly (OR 2.113, 95% CI 1.608-2.775, p<0.001).

In Chua M et al., study, the median length of hospital stay was 13 days and concluded that hyponatremia was strongly associated with longer hospital stay [10]. Authors found the median length of stay at six days (range: 1-52 days) in hyponatremia group in comparision to five days (range: 1-25) in normonatremic group with statistical significance (p<0.001).

However, authors could not find statistically significant difference in mortality across both the group though presence of underlying comorbid was a significant factor for hyponatremia; which may be an important limitation of the present study. Though, authors found a markedly high 8% of mortality in moderate hyponatremia than mild and severe hyponatremic patients (2.7%, 2.8%); was also statistically not significant (Fisher's-exact test, p=0.06). However, Chawla A et al., studied overall mortality rate among 45,693 hospitalized patients with hyponatremia (<135 mEq/L) compared with 164,146 patients with s. Na >135 mEq/L and concluded that severity of underlying illnesses rather than severity of hyponatremia is the responsible cause for death; propitiating the present findings [30]. Furthermore, Asadollahi K et al., found no consistent association of death with hyponatremia, after reviewing many literatures and analysing mortality pattern of 12 different studies [31].

LIMITATION

The present study did not measure serum sodium level of patients on daily basis. Hence, the true incidence of hyponatremia in patients during hospitalisation may be higher than the present report. Prognosis of hyponatremia in elderly patients, in terms of mortality rate, may be affected by confounding factors and age itself may be a confounder. To confer prognosis precisely, therefore, requires further statistical analysis like large scale regression analysis, which is another limitation of the present study. However, a large sample size and an appropriately matched control group for comparison, strengthen the present study.

CONCLUSION

Nearly half of the elderly patient has hyponatremia on admission and hypovolemic hyponatremia is a frequent type. Multifactorial aetiology is the most common cause and other leading causes are diuretic use, renal failure, and infection. Low salt intake and nutritional hypoalbuminemia, in combinations with other factors, also contribute to hyponatremia in elderly. Comorbids are often present in elderly patients and a significant risk factor for hyponatremia; especially the presence of multiple comorbids. Hyponatremia, in elderly patients certainly causes longer hospital stay but association with higher mortality rate is inconsistent, and needs further extensive study.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Oct 15, 2018**
Date of Peer Review: **Nov 15, 2018**
Date of Acceptance: **Dec 05, 2018**
Date of Publishing: **Feb 01, 2019**

Original Article

Prevalence and incidence of hyponatremia and their association with diuretic therapy: Results from North India

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Abstract

Introduction: Hyponatremia is associated with substantial morbidity and mortality. Correct estimation of their prevalence, incidence and risk factors, especially the diuretics in Indian patients is important in determining preventive strategies. **Methods:** This multistage mixed methods-based study was conducted in a high-volume cardiac care center to ensure the correct estimation. Patients receiving oral diuretics on an outpatient basis and those admitted to hospital for hyponatremia were enrolled. **Results:** The prevalence of hyponatremia was 27% while the incidence rate was 18% and 29% after 3- and 6-month of the diuretic therapy. The highest rates of hyponatremia were observed in warm season (45%, 111 in 247 patients). Multivariate logistic regression analysis revealed that low solute and nutritious intake and edematous state were negatively correlated with serum sodium levels. Neither diarrhea/vomiting nor diuretic use were found to be associated with hyponatremia. **Conclusions:** Diuretics use was not associated with hyponatremia in adults in this population cohort. However, elderly people on diuretics are comparatively more likely to have hyponatremia. However, a randomized parallel arm trial comparing diuretics with other antihypertensives be done to establish whether diuretics are associated with hyponatremia in this patient population.

Keywords: Loop diuretics, seasonal variation, serum sodium

Introduction

Hyponatremia is the most common electrolyte disorder ranging from 5.2 to 28.8% in hospitalized patients, with an average of about 25.98% for elderly patients experiencing this disorder.[1-3]

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Received: 01-08-2019 **Revised:** 21-08-2019
Accepted: 14-10-2019 **Published:** 10-12-2019

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_604_19

Hyponatremia is not a disease but rather a pathologic alteration in water homeostasis.[4] Causes of hyponatremia include certain drugs (such as hydrochlorothiazide), gastrointestinal loss, corticosteroid withdrawal, hypothyroidism, and the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[4]

In most cases, patients with hyponatremia are asymptomatic, but sometimes it may present with neurologic and gastrointestinal symptoms if serum sodium concentration drops below 120 mEq per liter.[5,6] Although the past several years have seen major progress in the field of hyponatremia, it remains unclear which factors mainly contribute to hyponatremia. Several studies have

How to cite this article: Singh A, Ahuja R, Sethi R, Pradhan A, Srivastava V. Prevalence and incidence of hyponatremia and their association with diuretic therapy: Results from North India. J Family Med Prim Care 2019;8:3925-30.

reported severe hyponatremia after the use of thiazide-type diuretic for hypertension.[7-9] However, most of these studies were performed in a non-controlled fashion or conducted in selected subpopulations.[7,9] Since diuretics are still recommended as first line treatment for hypertension, it is important to identify the risk factors associated with the development of hyponatremia.

Primary care physicians (PCPs) play an extremely important role as they are often the initial point of contact for patients in obtaining the treatment for common electrolyte disorder including hyponatremia. So, knowledge regarding the risk factors for hyponatremia and their treatment is very important as advice from PCPs has been shown to influence behaviors.[10]

The aim of this research was to undertake the most detailed study to date on the etiology of hyponatremia in general Indian population and report its prevalence, incidence, and correlation with risk factors, specially the diuretic. This study used multistage mixed methods to estimate (prevalence, incidence) and test in a case control study the correlation between various risk factors and the hyponatremia.

Methods

This multistage mixed methods study was carried out in Gandhi Memorial (GM) and Associated Hospitals, King George's Medical University (KGMU), Lucknow from over a period of one year. Informed consent was obtained from all participants. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the GM and Associated Hospitals, KGMU, Lucknow, in accordance with its guidelines for the protection of human subjects.

In the first stage, the study assessed the prevalence of hyponatremia through cross-sectional survey of anationally representative sample (Prevalence survey). In the second stage, the incidence of hyponatremia was recorded in patients started on diuretics for edematous disorders (Incidence study). In the third stage, a case control study was conducted to assess the independent association between various risk factors and the incidence of hyponatremia (Case-control study).

Study population

Prevalence survey (Stage 1)

Those >18 years of age, treated with diuretics for ≥6 months and attending the Medicine OPD/consultant's office of G.M. and Associated Hospitals were included in the survey.

Incidence study (Stage 2)

This prospective study was conducted in the patients attending the Medicine OPD/consultant's office of G.M. and Associated Hospitals and those discharged from G.M. and Associated Hospitals.

Case-control study (Stage 3)

Patients aged ≥18 years with moderate-to-severe hyponatremia (<135 mEq/L) admitted to the medical ward were included in the study. The exclusion criteria comprised of cases with hyperglycemia, hyperlipidemia, and paraproteinemia. Age and sex matched patients with normal serum sodium levels hospitalized in medical ward during same period for any illness and consenting to participate constituted the controls for case control study.

Data collection

This study used a case report form (CRF) that included four major sections. The first section included demographics and the status of the patient at the time of inclusion (outpatient). In the second section of the CRF, several questions regarding diagnosis, degree of physical activity, and number of visits to medical OPD were included. The third section of the CRF included several questions about the pharmacotherapy. In the fourth and last section of the CRF, the results of the following tests (at baseline, 3-months and 6-months): serum sodium, serum potassium were requested.

Prevalence survey (Stage 1)

Age, gender, physical activity and diuretic therapy were determined from CRF questionnaires. Primary outcome variable was hyponatremia in those receiving diuretics >6 months. We attempted to identify patients with several co-morbidities using a combination of laboratory results, and responses to disease specific questions. Specifically, we identified participants who were using diuretics for various conditions including hypertension, diabetes, congestive heart failure, coronary artery disease, hypersensitivity pneumonitis, chronic lung disease, chronic renal failure, and chronic obstructive pulmonary disease etc., Participants with hypernatremia, defined as sodium above the reference ranges, were excluded.

Incidence study (Stage 2)

Those >18 years of age started newly on diuretics and will continue for at least 6 months for edematous disorders were included in the study. Participants with hypernatremia were excluded. Primary outcome variable was development of hyponatremia in these patients. Data on demographics, co-morbid conditions, type and number of diuretic agents and impact of seasonal variation was recorded by trained data collectors on CRF. A history of physician-diagnosed hypertension, diabetes, congestive heart failure, coronary artery disease, hypersensitivity pneumonitis, chronic lung disease, chronic renal failure, and chronic obstructive pulmonary disease was noted.

Case-control study (Stage 3)

All adult inpatients (>18 years) with mild, moderate or severe hyponatremia (serum sodium ≤135 mEq/L) were eligible for inclusion in the study. Controls were defined as those received hospital treatment for any other illness and not for hyponatremia (serum sodium >135 mEq/L). Cases and controls were comparable in terms of sex and age group, and who gave written consent. Patients who refused participation in the study or had cognitive impairment, were excluded from the study. Each patient data was considered only once. The frequency of

laboratory tests or the treatments of hyponatremia were not affected by the study.

Statistical analysis

Statistical analyses were performed using STATA 9.2. Categorical variables were presented as numbers and percentages, while continuous variables as mean ± SD. Student's *t*-test was used for assessing change from baseline in continuous variables and Chi square test compared categorical variables. We performed univariate logistic regression analysis to determine the association between clinical variables and hyponatremia following diuretic therapy. We also performed univariate and multivariate logistic regression analyses in case control study to determine the association between clinical variables and hyponatremia. *P* value less than 0.05 was considered to be statistically significant.

Results

Prevalence survey (Stage 1)

The population (n = 109) had a mean age of 48.6 years and was largely male (64.2%). 29% of patients were sedentary while 71% were physical active. Most patients (50/109 [45.9%]) were receiving thiazide diuretics followed by loop diuretics in 39 patients (35.8%). Twenty patients were taking two diuretic agents concomitantly, the most frequent combination being loop diuretics and potassium sparing diuretics (n = 16). The major indication for diuretics was hypertension alone (20.2%), followed by hypertension and diabetes mellitus (12.8%), hypertension and coronary artery disease (11.0%), congestive heart failure (CHF; 9.2%), chronic liver diseases (CLD; 7.3%), and others (39.5%), respectively. Hyponatremia was present in 29 (27%) patients. Of these, 13 patients had mild hyponatremia and 16 had moderate hyponatremia [Figure 1]. No one had severe hyponatremia. In addition, hypokalemia was present in 8 (7%) patients. Univariate logistic regression analysis demonstrate an increase in the prevalence of hyponatremia with age ($P = 0.0023$) and during heat periods ($P = 0.012$).

Incidence study (Stage 2)

A total of 87 patients were included. The mean age at presentation was 50 ± 10 years and 63% were men. Of the 87 patients, 44 (51%) had documented peripheral edema. 38% patients were sedentary while 62% were physical active. 36% (n = 31) patients were prescribed with loop diuretics followed by 34% (n = 30) receiving thiazides, and 14% (n = 12) receiving potassium sparing diuretics. Twelve patients (14%) used a combination of loop diuretics and potassium sparing diuretics. In addition, one patient used a combination of thiazide and potassium sparing diuretics and other one used combination of thiazide and loop diuretics. Diuretics were prescribed mainly for hypertension (51%) in patients with non-edematous disorders while CHF was the most common (30%) reason for their use in patients with edematous disorders. A significant decrease was found in mean serum sodium levels after 3-and 6-months of diuretic therapy (138.5 ± 2.5 mEq/L vs. 136.7 ± 3.4 mEq/L and 135.5 ± 4.5 mEq/L; $P < 0.0001$). Total 16 (18%) and 25 (29%) patients experienced hyponatremia after 3- and 6-month of the therapy. Also, 3% and 10% experienced hypokalemia, respectively. Univariate logistic regression analysis demonstrated an increase in the incidence of hyponatremia with edematous disorders ($P = 0.0390$). Neither age ($P = 0.134$) nor physical activity ($P = 0.459$) was associated with hyponatremia.

Case-control Study (Stage 3)

A total of 247 cases and 247 controls were matched using a 1:1 ratio for gender (38% female, 62% male). Most of the patients were aged between 35 and 65 years. The mean age was 50.3 ± 15.5 years for cases and 48.6 ± 12 years for control [Table 1].

Out of 247 hyponatremic patients, 106 patients (43%) had a serum sodium of 130-134 mEq/L while 125 (51%) had 120-129 mEq/L. Severe hyponatremia (serum sodium < 120 mEq/L) was detected in 16 patients (6%). Hypokalemia (<3.5 mEq/L) was seen in 27% (95% CI; 22-34) cases. Patients with hyponatremia were older and more likely to have edematous states, more severe symptoms of diarrhea/vomiting and frequent use of diuretics.

Hyponatremia and seasonal variation

The prevalence of patients with profound hyponatremia (<135 mmol/l) in each month is shown in Figure 2. The incidence was 24.3% between January and March, 44.9% between April and June, 8.5% between July and September and 22.3% between

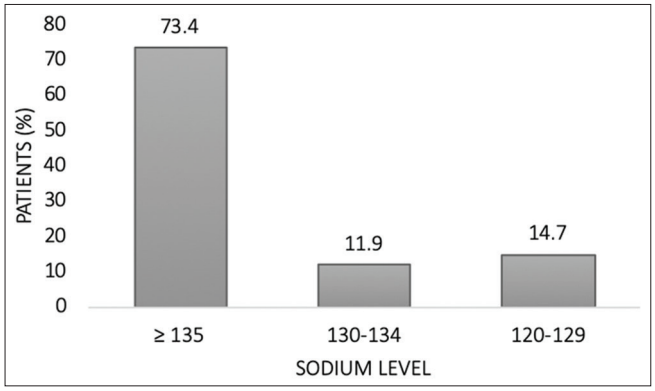

Figure 1: Distribution of serum sodium in the study population

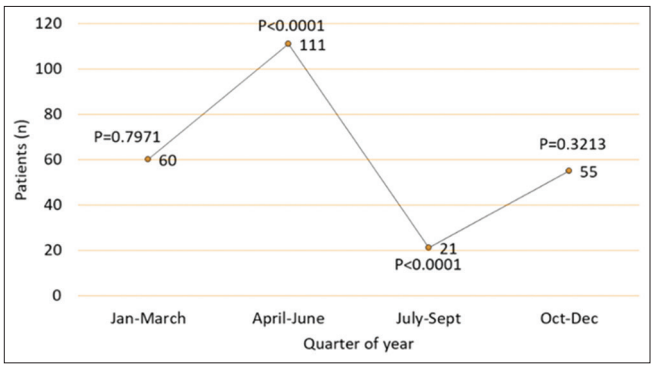

Figure 2: Seasonal variation and prevalence of hyponatremia

October and December. Statistically significant difference was observed in incidence rate of hyponatremia between second quarter (Apr-June months) and third quarter (Jul-Sep months) of the year ($P < 0.0001$). Thus, the prevalence of hyponatremia in the warm season of April to June (44.9%, 111 in 247 patients) was significantly ($P < 0.0001$) higher than that in the rainfall season (9%, 21 in 247 patients) and the cold season of October to March (46.6%, 115 in 247 patients).

Risk factors for developing hyponatremia

Univariate and multivariate logistic regression analyses were performed to evaluate the determinants of hyponatremia. Table 2 lists the results of both logistic regression analyses. In univariate analysis, diuretics use, presence of diarrhea/vomiting, poor solute and nutrients intake, and edematous states were significantly associated with hyponatremia [Table 1]. Patients on diuretics increased their risk by 160%. Conditions like diarrhea/vomiting increased risk by 250%, edematous states by 620%, and poor solute and nutrients intake by 200%. However, in the multivariate analysis, only poor solute and nutrients intake (2.2; $P = 0.010$) and edematous states (6.40; $P = 0.001$) were independently associated with the development of hyponatremia (acute hospital population). Neither diarrhea/vomiting ($P = 0.287$) nor diuretics use ($P = 0.664$) was associated with hyponatremia [Table 2].

Discussion

The multistage study method is the most general framework among advanced designs. We report, for the first time in India, the prevalence, incidence and correlation of various risk factors with hyponatremia in a multistage design and establish that diuretics are not associated with hyponatremia in adult patients, after controlling the confounding factors. The study estimated prevalence and incidence of hyponatremia in separate samples of general Indian population receiving regular diuretics for at least 6 months in ambulatory settings. Univariate analysis of stage 3 case control study demonstrates an increase in the prevalence of hyponatremia with diuretic use, diarrhea/vomiting, low solute and nutritious intake, and edematous states. However, multivariate analysis determined that only subjects with low solute and nutrients intake and edematous states were significantly more likely to have hyponatremia. Neither diarrhea/vomiting nor diuretic use were found to be associated with hyponatremia.

Table 1: Demographic details in the case control study

	Cases (*n*=247)	Control (*n*=247)
Age (mean±SD)	50.3±15.5	48.6±12
Male [*n* (%)]	153 (62)	153 (62)
Female [*n* (%)]	94 (38)	94 (38)
Physical activity		
Sedentary [*n* (%)]	60 (24)	63 (26)
Moderate [*n* (%)]	187 (76)	184 (74)

Table 2: Predictors of developing hyponatremia by logistic regression analysis

Risk factors	Odds ratio	95% CI	*p*
Univariate logistic regression analysis			
Diuretic use (yes vs. no)	1.6	1.1-2.4	<0.0001
Diarrhea/vomiting (yes vs. no)	2.5	1.2-5.0	0.0063
Poor solute and nutrients intake (yes vs. no)	2.0	1.1-3.8	0.0236
Edematous states (yes vs. no)	6.2	3.4-11.7	<0.0001
Multiple logistic regression analysis			
Diarrhea/vomiting	1.5	0.7-2.9	0.287
Poor solute and nutrients intake	2.2	1.2-4.0	0.010
Edematous states	6.40	3.4-12.2	0.001
Diuretics use	0.90	0.6-1.43	0.664

The prevalence rate of hyponatremia in our study was 27%, which is consistent with the previous findings that have estimated the prevalence of hyponatremia to 5.2%-28.8% of Indian patients admitted to hospitals.[1-3] According to a study from the Netherlands in 2013, the prevalence of hyponatremia was 7.7%, a marked less prevalence rate from the 27% reported in our study.[11] The larger prevalence obtained in Indian studies may be attributed to inadequate nutrition and low solute intake as well as tropical weather conditions. In 2002, Chakrapani *et al.* from India reported the important role of humidity and temperature in the manifestation of hyponatremia.[12] During the study period of two years, they found an increased incidence of hyponatremia in the peak southwest monsoon season.[12] In contrast, our study reported higher incidence of hyponatremia during the warm season of April to June (45%, 111 in 247 patients) than in the rainfall season (9%, 21 in 247 patients). Studies from Switzerland and Japan have also reported a higher risk of hyponatremia during the hot weather.[13,14] So we could validate the prevalence and incidence in separate groups of population through multistage design.

Previous studies have shown higher risk of hyponatremia in patients using certain drugs (e.g. diuretics, antidepressants, antiepileptics, tramadol, and codeine) and those with compromised age-related physiology and multiple comorbidities.[15,16] In 2018, a study by Imai *et al.* reported significantly higher prevalence of hyponatremia in the elderly group than in the adult group (17.0% vs. 5.7%, $P < 0.001$).[17] However, several studies suggest that age alone does not appear to be an independent risk factor for hyponatremia after controlling all other confounding variables.[18,19] A study by Al Mawed *et al.* has shown significantly higher hyponatremia-associated mortality in younger versus older patients.[20] In order to identify more reliable and validated risk factors for hyponatremia, both univariate and multivariate logistic regression analyses were performed in our matched case–control study (stage 3). Univariate analysis found hyponatremia to be elevated in subjects with edematous states, diarrhea/vomiting, low solute and nutrients intake, and those using diuretics.

The cause of hyponatremia may be renal (nephritis, diuretics, mineralocorticoid deficiency) and/or extrarenal (vomiting, diarrhea, burns).[21] Hyponatremia due to water excess is attributable to heart failure, nephrotic syndrome, cirrhosis and

others (infusion 5% glucose solutions and drugs that stimulate antidiuretic hormone (ADH) secretion).[21] In our study, subjects with edematous states were significantly more likely to have hyponatremia compared to those without edematous states meaning that edematous states had lower levels of serum sodium.

Hyponatremia due to poor solute and nutrients intake is described only in individual case reports.[22] In 1972, Gwinup *et al.* found that administration of more than 5 liters of beer daily for seven days results in hyponatremia, weight gain, strongly positive fluid balance and inappropriate urinary concentration.[23] Both American (2013) and European (2014) clinical practice guidelines considered urine osmolality of <100 mOsm/kg in hyponatremia and low dietary solute intake as a major cause of this condition.[24,25]

Thiazide type diuretics are associated with an increased risk of hyponatremia.[26] In 2006, a study that prospectively looked at patients hospitalized with severe hyponatremia; a greater proportion of patients were on loop diuretics than thiazides.[27] In consistent with these previous studies, diuretics use ($P = 0.664$) was also found not to be associated with hyponatremia in multivariate analysis of our study; though several study considered thiazide type diuretics as a major cause of hyponatremia.

Multivariate logistic regression analysis of our case-control study also suggested that if all other confounding factors are controlled, then only edematous disorders states, and poor salt and nutrients intake seem to be independent risk factors for development of hyponatremia. This is also in agreement with the results of previous studies showing that patients with diuretic hyponatremia frequently have other conditions like hot weather contributing to the hyponatremia.[14,28,29] Thus, it is fair to conclude that diuretics may be associated with hyponatremia but do not directly cause it.

The strength of the study is the multistage mixed methods design, and separate population evaluation leading to large sample size. To the best of our knowledge, this is the first Indian study to systematically evaluate and quantify various risk factors for hyponatremia in patients taking diuretic therapy. The study differs from already published case reports detailing limited number of severe hyponatremic cases. Also, this study describes the risk factors with certainty in both ambulatory and hospital settings; though this is a fundamental difficulty in the geriatric population. However, the study has several methodological limitations. Firstly, information regarding the different dosages of diuretics has not been recorded which may be a confounder. Secondly, contribution of other agents causing hyponatremia like other medications causing hyponatremia has not been recorded.

Conclusion

It is concluded that diuretics are not associated with hyponatremia in adult patients in this cohort of patients. However, elderly population on diuretics is more likely to have hyponatremia compared to the adult population. The authors recommend that a randomized parallel arm trial comparing diuretics with other antihypertensives be done to establish whether diuretics are associated with hyponatremia in this patient population.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Nephrol Dial Transplant (2012) 27: 891–898
doi: 10.1093/ndt/gfs038

NDT
Nephrology Dialysis Transplantation

Editorial Review

Significance of hypo- and hypernatremia in chronic kidney disease

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Abstract
Both hypo- and hypernatremia are common conditions, especially in hospitalized patients and in patients with various comorbid conditions such as congestive heart failure or liver cirrhosis. Abnormal serum sodium levels have been associated with increased mortality in numerous observational studies. Patients with chronic kidney disease (CKD) represent a group with a high prevalence of comorbid conditions that could predispose to dysnatremias. In addition, the failing kidney is also characterized by a gradual development of hyposthenuria, and even isosthenuria, which results in further predisposition to the development of hypo- and hypernatremia in those with advancing stages of CKD. To date, there has been a paucity of population-wide assessments of the incidence and prevalence of dysnatremias, their clinical characteristics and the outcomes associated with them in patients with various stages of CKD. We review the physiology and pathophysiology of water homeostasis with special emphasis on changes occurring in CKD, the outcomes associated with abnormal serum sodium in patients with normal kidney function and the results of recent studies in patients with various stages of CKD, which indicate a substantial incidence and prevalence and significant adverse outcomes associated with dysnatremias in this patient population.

Keywords: chronic kidney disease; hypernatremia; hyponatremia; mortality; serum sodium

Introduction

Hyponatremia is one of the most common electrolyte abnormalities encountered in clinical practice, occurring in as many as 42% of acutely hospitalized patients [1]. Hyponatremia is associated with many different disease states such as congestive heart failure (CHF), liver cirrhosis, pneumonia and acquired immune deficiency syndrome, and is regarded as an important marker of the severity of these conditions [2, 3]. Other risk factors of hyponatremia are advanced age [1], male gender[1], low body weight [4, 5] and in nursing home populations also hypotonic fluid intake, low-sodium diet and tube feeding [6]. Both hypo- and hypernatremia are associated with significant increases in mortality in hospitalized patients and in patients with various comorbid conditions [7–28]. The development of vasopressin receptor antagonist medications that are able to induce a selective water diuresis without affecting sodium excretion [29] has led to renewed interest in the link between hyponatremia and various adverse outcomes. These medications have been shown to reliably correct hyponatremia [30–33], and hence could represent therapeutic options for patients under a variety of circumstances.

Chronic kidney disease (CKD) is known to affect the ability of the kidneys to regulate water homeostasis [34], and hence the risk of both hypo- and hypernatremia can increase with advancing stages of CKD. In spite of such physiological considerations, the results of earlier small observational studies suggested that frank hypo- or hypernatremia resulting from advancing CKD alone are rare or even non-existent even in patients with very advanced stages of non-dialysis-dependent CKD [35]. However, there has been a lack of population-level surveys of the incidence and/or prevalence of hypo- or hypernatremia in patients with CKD. It has also been unclear to what extent dysnatremias are associated with outcomes in patients with various stages of non-dialysis-dependent CKD. Due to their high numbers and their particular disease characteristics that predispose them to dysnatremias, patients with CKD represent a large and under-studied group in whom the characteristics and the consequences of both hypo- and hypernatremia still need to be clarified. In this review, we discuss briefly the physiology and pathophysiology of water homeostasis, the consequences of hypo- and hypernatremia in patients with normal kidney function and recent findings regarding the characteristics and outcomes associated with dysnatremias in patients with various stages of CKD.

Physiological background and significance of dysnatremias in patients with normal kidney function

Sodium is the most abundant electrolyte in the extracellular fluid, and it is the main contributor to extracellular tonicity

[36]. The physiological regulation of serum sodium level is maintained by balancing water intake and water excretion; the former through control of thirst sensation and the latter through control of antidiuretic hormone (ADH) secretion [36]. The ADH vasopressin (VP) [37] stimulates the plasma membrane accumulation of a water channel, aquaporin 2, which is a member of a family of water channel molecules that is located primarily in the kidney collecting duct principal cells [38]. The accumulation of aquaporin 2 in the collecting duct epithelium increases its water permeability, allowing osmotic equilibration of the luminal fluid with the surrounding interstitium and leading to urinary concentration [39].

Water balance can be disturbed by pathological states causing either abnormal water intake (through disordered thirst sensation or impeded access to water), changes in ADH secretion that override the primary osmotic stimulus for this hormone or abnormalities involving the VP receptor or aquaporin 2 in the collecting duct [40]. The resulting water excess or deficit leads to abnormal dilution or concentration of the extracellular fluid, most readily measured through concentration changes of serum sodium and hence resulting in hypo- or hypernatremia. As a result of such alterations in extracellular tonicity, a concentration gradient may occur between the intra- and extracellular space especially after rapidly developing hypo- or hypernatremia with water shifts leading to cellular swelling or shrinking. The physiological consequences of this are most acutely recognized in the central nervous system, where they could lead to potentially fatal brain edema or osmotic demyelination syndrome, respectively [41–43]. The impact of transcellular water shifts on the structure and function of organs whose cells are not limited to a closed space such as the cranium is less clear, but there have been suggestions that hyponatremia could be implicated in bone fractures [44–46], rhabdomyolysis [47], CHF and/or pulmonary edema [48, 49].

Based on these physiological considerations, it is plausible to postulate that both hypo- and hypernatremia can lead to adverse clinical consequences and potentially result in increased deaths, especially if they occur acutely. Outcomes associated with abnormal serum sodium levels have been explored by a substantial number of observational studies [7–28], mostly in the setting of acute hospitalization, or in patient populations known to be at risk for the development of abnormal serum sodium levels (such as patients with CHF or liver cirrhosis) (Table 1). The majority of these observational studies focused on the association of hyponatremia with outcomes such as mortality. Lower serum sodium levels have been associated with adverse clinical outcomes in most of the studies, independent of the presence of various confounders (Table 1). Hypernatremia has been generally under-emphasized, but it has also been found to be associated with a significant increase in mortality (Table 1) [7, 14].

In spite of the robust association of hypo- and hypernatremia with outcomes such as mortality, one cannot determine with certainty to what extent these associations may be biased by unmeasured confounders, especially since abnormal ADH secretion and consequently hyponatremia can occur as a result of various stress stimuli that can be difficult to quantify in observational studies. The emergence of specific pharmacologic inhibitors of the vasopressin receptor [29] has allowed the testing in clinical trials of the hypothesis that hyponatremia is causally involved in excess mortality, and hence its correction results in improved clinical outcomes. The short-term administration of vasopressin receptor antagonists was shown to result in a predictable correction of hyponatremia [30–33] and improvement in peripheral edema and various other clinical features of CHF [50, 51]. Based on such results, the Efficacy of Vasopressin antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial was designed to test the hypothesis that correction of hyponatremia using tolvaptan (an oral selective V2 receptor antagonist [30]) versus placebo therapy on top of routine medical management of patients hospitalized with CHF results in improved all-cause mortality, cardiovascular mortality or CHF-related hospital admissions [52]. This study included 4133 patients treated with tolvaptan versus placebo for a minimum of 60 days and showed that none of the primary end points of the study were affected significantly by such treatment. While the results of the EVEREST study appear to refute the hypothesis invoking hyponatremia as a cause of increased mortality in CHF, it is unclear how the correction of hyponatremia would impact outcomes under different circumstances; patients with more severe hyponatremia or patients with hyponatremia unrelated to CHF may respond differently to the same treatment, and the longer duration of therapy with the same drug or effect of other interventions to correct hyponatremia may also result in different outcomes. At the present time, medical interventions including vasopressin receptor antagonists are indicated only for the correction of a biochemical abnormality (hyponatremia) but without a clear understanding of their impact on longer-term outcomes.

Water homeostasis, hyponatremia and hypernatremia in CKD

With advancing CKD, the kidney has a remarkable ability to maintain homeostasis, including the regulation of water balance [34]. In a study of 70 patients with advanced CKD (serum creatinine levels >10 mg/dL), serum sodium levels remained normal even until the point of the patients requiring initiation of renal replacement therapy [35]. The ability of the kidneys to adapt to changes in water intake does, however, diminish as both the maximum dilution and concentration of the urine gradually decline during the course of CKD (hyposthenuria), with the capacity to dilute typically being maintained longer than the capacity to concentrate [53]. Ultimately, as the patients reach end-stage kidney failure, the urine osmolality remains constant at ~300 mOsm/L (isosthenuria) irrespective of the actual volume of water intake. As a result, physiological factors other than the amount of water intake and urinary dilution and concentration will determine the amount of excreted water, and hence the development of hypo- and hypernatremia in patients with CKD. These include the amount of water delivered from the proximal tubule (which is typically decreased as a result of low glomerular filtration rate) and the amount of excreted solute, which can facilitate the development of both hypo- and hypernatremia in patients with

Table 1. Studies examining outcomes associated with serum sodium level in patients with normal kidney function[a]

Study	Patient population	Results	Other findings
Wald *et al.* [7]	$N = 53\,236$ patients hospitalized at a single medical center	Hyponatremia associated with increased mortality and length of stay and increased risk of discharge to a long-term facility. Hypernatremia also associated with higher mortality	Equal incidence of community and hospital-acquired hyponatremia (37.9 and 38.2%)
Waikar *et al.* [8]	$N = 98\,411$ patients admitted to two hospitals	Higher 1- and 5-year mortality risk associated with hyponatremia	Incidence of hyponatremia of 14.5%
Zilberberg *et al.* [9]	$N = 198\,281$ hospitalizations from 39 US hospitals	Hyponatremia associated with increased mortality, ICU admissions, mechanical ventilation, hospital length of stay and cost of care	Incidence of hyponatremia was 5.5%
Tierney *et al.* [10]	$N = 13\,979$ patients admitted over 46 months	Hyponatremia associated with increased in-hospital and long-term mortality	Incidence of hyponatremia at admission was 4%
Gill *et al.* [11]	$N = 104$ hyponatremic hospitalized patients compared to $N = 104$ randomly chosen normonatremic patients	Mortality and length of stay higher in the hyponatremic group	Mortality was higher if serum sodium fell during hospitalization
Clayton *et al.* [12]	$N = 108$ hospitalized patients with serum sodium <125 mEq/L compared to normonatremic patients	Mortality was higher in the hyponatremic group	Mortality depended on the etiology and not the severity of the hyponatremia
Lee *et al.* [13]	$N = 3784$ patients admitted to en emergency department	Lower serum sodium was associated with higher mortality	3.8% of patients had serum sodium <134 mEq/L. Most hyponatremic patients had hypovolemia
Mohammed *et al.* [14]	$N = 628$ patients presenting to an emergency department with decompensated CHF	Both hyponatremia and hypernatremia were associated with higher 1-year mortality rates	24% of patients had serum sodium <135 mEq/L. Lower serum sodium was associated with higher NT-proBNP levels
Gheorghiade *et al.* [15]	$N = 48\,612$ patients hospitalized with CHF from 259 hospitals	Hyponatremia associated with higher in-hospital and follow-up mortality and longer hospital stay	19.7% of patients had serum sodium <135 mEq/L
Gheorghiade *et al.* [16]	*Post hoc* analysis of $N = 433$ patients hospitalized with Stage 4 CHF and enrolled in a clinical trial	Persistent hyponatremia independently associated with increased mortality and re-hospitalization	23.8% of patients had hyponatremia; of these 68.9% had persistent hyponatremia
Rossi *et al.* [17]	*Post hoc* analysis in $N = 319$ hospitalized CHF patients treated with tolvaptan versus placebo	Significantly lower mortality of patients who had improvement in serum sodium levels	21.6% of patients had hyponatremia
Klein *et al.* [18]	*Post hoc* analysis in $N = 942$ hospitalized CHF patients treated with milrinone versus placebo	Lower sodium associated with increased in-hospital and 60-day mortality	Patients with lower serum sodium had more severe CHF
Lee *et al.* [19]	$N = 203$ patients with severe CHF	Hyponatremia was associated with increased CV mortality	Hyponatremic patients treated with ACEI had better outcomes
Goldberg *et al.* [20]	$N = 978$ patients with ST-elevation MI and no CHF	Hyponatremia associated with increased mortality and hospital readmission rates	11% of patients had serum sodium <136 mEq/L
Goldberg *et al.* [21]	$N = 1047$ patients with acute ST-elevation MI	Hyponatremia associated with increased 30-day mortality	12.5% of patients had serum sodium <136 mEq/L on admission and developed in 19.9% within 72 h

Continued

Table 1. *Continued*

Study	Patient population	Results	Other findings
Zilberberg *et al.* [22]	$N = 7965$ patients hospitalized with pneumonia	Hyponatremia associated with increased mortality, ICU admissions, mechanical ventilation, hospital length of stay and cost of care	8.1% of patients with pneumonia had hyponatremia
Borroni *et al.* [23]	$N = 156$ hospitalized patients with liver cirrhosis	Hyponatremia was associated with increased short-term mortality	29.8% of patients had hyponatremia
Lim *et al.* [24]	$N = 837$ patients listed for liver transplantation	Serum sodium level was not an independent predictor of mortality once adjusted for effect of GFR	GFR was measured by iothalamate clearance
Londono *et al.* [25]	$N = 241$ patients who received a liver transplant	Hyponatremia at the time of transplantation predicted 90-day post-transplant mortality	Long-term survival was not affected by serum sodium level
Heuman *et al.* [26]	$N = 507$ patients referred for liver transplantation	Hyponatremia was associated with higher mortality only in patients with MELD score <21	Persistent ascites and MELD score also predictive of mortality
Terzian *et al.* [27]	$N = 4123$ hospitalized elderly patients	Hyponatremia was independently associated with increased in-hospital mortality	Prevalence of hyponatremia was 3.5%
Bennani *et al.* [28]	$N = 2188$ patients admitted to an intensive care unit	Sodium <125 mEq/L was an independent predictor of mortality	Incidence of hyponatremia was 13.7%

[a]CV, cardiovascular; ICU, intensive care unit; MELD, model for end-stage liver disease; MI, myocardial infarction; NT-proBNP, amino-terminal pro-B-type natriuretic peptide.

advancing CKD irrespective of the actual urine osmolality [54].

To the best of our knowledge, the incidence and prevalence of hypo- and hypernatremia in patients with different stages of CKD have not been studied at a population level until recently. In a recent study of 655 493 US veterans with non-dialysis-dependent CKD, the point prevalence of hyponatremia (serum sodium <136 mEq/L) was 13.5% and the point prevalence of hypernatremia (serum sodium of >145 mEq/L) was 2% [55]. During a mean duration of follow-up of ~5 years, however, 26% of all patients developed at least one episode of hyponatremia and 7% had at least one episode of hypernatremia, suggesting that these conditions and especially mild hyponatremia are common occurrences in patients with CKD. As shown in Figure 1A, the prevalence of hyponatremia did not correlate with the stage of CKD as it was essentially identical in patients with CKD Stages 3A and above. The prevalence of hyponatremia was higher in patients with CKD Stages 1 and 2, in whom the definition of CKD included the presence of significant proteinuria [56]. The prevalence of hypernatremia was about a magnitude lower overall compared to the prevalence of hyponatremia, but showed a significant increase with advancing stages of CKD (Figure 1B), supporting the observation that the kidney's concentrating ability is affected to a greater extent by advancing CKD than its diluting ability [53]. Overall, however, the prevalence of hyponatremia was significantly higher at all stages of CKD compared to the prevalence of hypernatremia.

The clinical characteristics associated with hyponatremia in our study were younger age, presence of diabetes mellitus, CHF, liver disease and depression, a higher estimated glomerular filtration rate (eGFR), blood glucose and white blood cell count and a lower serum albumin and blood hemoglobin. Characteristics associated with hypernatremia on the other hand were older age and lower eGFR, serum total bilirubin and blood glucose [55]. These results suggest that hypo- and hypernatremia may be affected by both the process of CKD and by the concomitant comorbidities occurring in patients with CKD. This study did not separate laboratory results obtained during an inpatient hospitalization versus an outpatient visit; hence it is unclear what the circumstances of occurrence were for these abnormalities.

Outcomes associated with hypo- and hypernatremia in CKD

Both hypo- and hypernatremia are associated with increased mortality in patients with normal kidney function (vide supra). These results should not be extrapolated to patients with various degrees of severity of CKD as it is unclear how the hypo- and isosthenuria developing with advancing CKD affect these outcomes when combined with various comorbid conditions that can impact water metabolism and outcomes. It is possible that hypo- and hypernatremia are more severe in CKD and hence they could be more deleterious; one could, however, also hypothesize that the chronic nature of the abnormalities affecting water metabolism in CKD allows the body to adapt

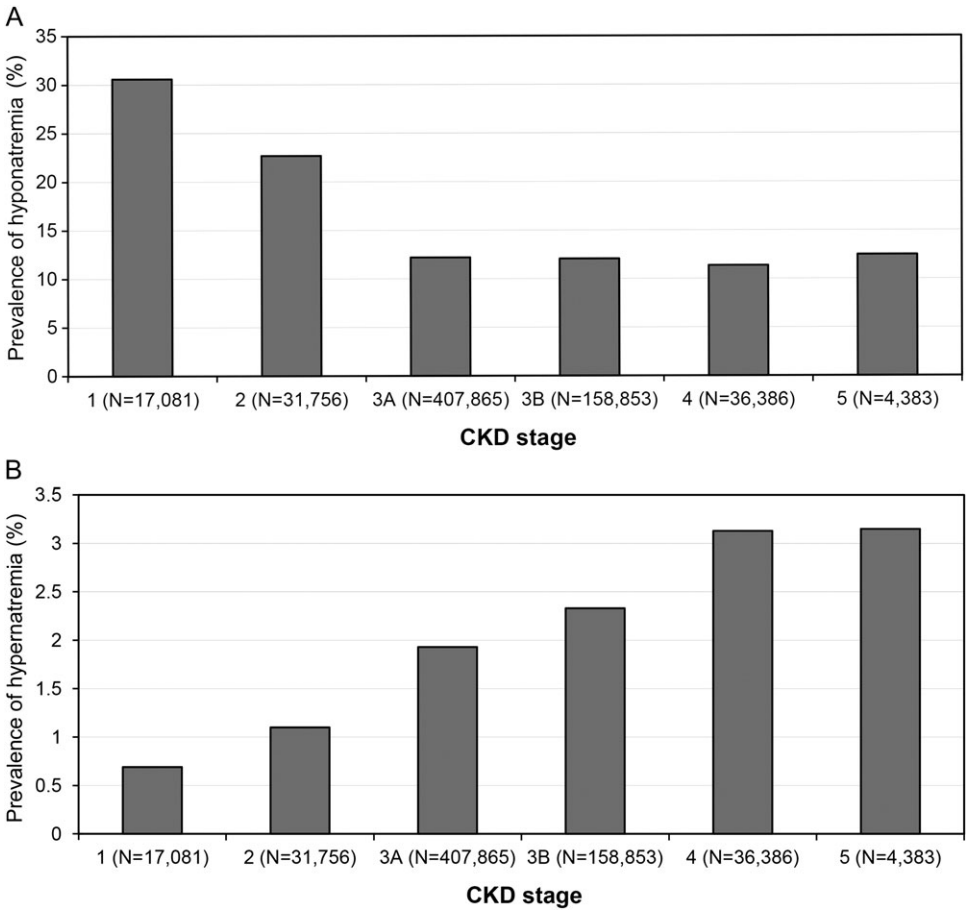

Fig. 1. Prevalence of hyponatremia (**A**) and hypernatremia (**B**) in patients with different stages of CKD in 655 493 US veterans with non-dialysis-dependent CKD. Results are based on data obtained from [55]. Note the different scales in the two panels.

to these consequences and hence their effects on outcomes could be diminished. We have recently examined the association of serum sodium levels with all-cause mortality in 655 493 US veterans with non-dialysis-dependent CKD Stages 1–5 (mean ± SD age was 73.9 ± 9.8 years, 87 and 9% of patients were white and black, respectively, and mean eGFR was 50.2 ± 14.1 mL/min/1.73 m^2) [55]. Both lower and higher time-varying serum sodium levels were associated with a significant increase in mortality, even after adjustment for various potential confounders (Figure 2). Mortality was lowest in patients with serum sodium levels in the 140–144 mEq/L range and showed a linear increase with increasing degree of severity of hypo- and hypernatremia. The association of hypo- and hypernatremia with mortality was present in all examined subgroups, including patients with and without CHF or liver cirrhosis [55], and also in patients with various stages of CKD (Figure 3). The magnitude of the association between hyponatremia and mortality did not appear to vary according to the severity of CKD (Figure 3). Interestingly, the association between hypernatremia and mortality appeared to diminish linearly with more advanced stages of CKD (Figure 3) [55]. The significance of this latter observation is unclear but suggests that perhaps there is indeed an element of adaptation to increased extracellular osmolality in patients with more advanced stages of CKD. As we mentioned previously, our study did not record the circumstances of serum sodium measurement (inpatient hospitalization versus outpatient), hence it is unclear to what extent the observed associations occurred in the context of acute illnesses. When comparing in parallel the associations of baseline serum sodium on longer term outcomes with the associations of time-varying serum sodium on short-term outcomes, the latter clearly showed much more robust associations [55], indicating that abnormalities in serum sodium are indeed either causing acute complications leading to higher short-term mortality or are simply potent surrogate markers of acute illness. Due to the observational nature of our study, we cannot establish causality in spite of the extensive adjustment for various potentially confounding comorbid conditions; such causality can only be proven if interventions of correcting serum sodium levels are shown to result in improved outcomes in CKD patients. Arguing in favor of a potential causal effect of dysnatremias on mortality was a recent study of maintenance hemodialysis patients enrolled in the Hemodialysis (HEMO) study, which reported a significant association of hyponatremia with mortality, even though in anuric dialysis patients the development of hyponatremia is unrelated to the pathological stimulation of ADH by underlying comorbidities [57]. Nevertheless, since in the anuric population, pre-dialysis hyponatremia could be a surrogate

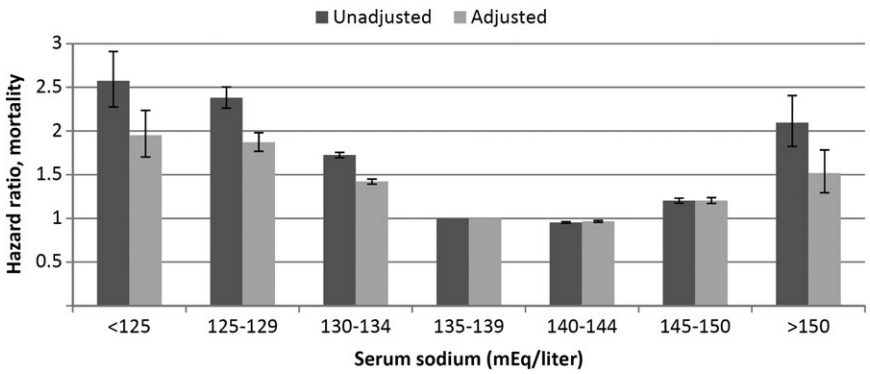

Fig. 2. Unadjusted and multivariable adjusted hazard ratios (95% confidence intervals) of all-cause mortality associated with various categories of serum sodium level in 655 493 US veterans with non-dialysis-dependent CKD. The group with serum sodium level of 135–139 mEq/L served as referent. Estimates are from time-dependent Cox model; multivariable adjusted models were adjusted for age, gender, race, geographic location, diabetes mellitus, atherosclerotic cardiovascular disease, CHF, liver disease, malignancy, depression, the Charlson comorbidity index, systolic blood pressure, eGFR, serum albumin, alkaline phosphatase, aspartate and alanine aminotransferases, total bilirubin, blood hemoglobin, glucose and white blood cell count. Results are based on data obtained from [55].

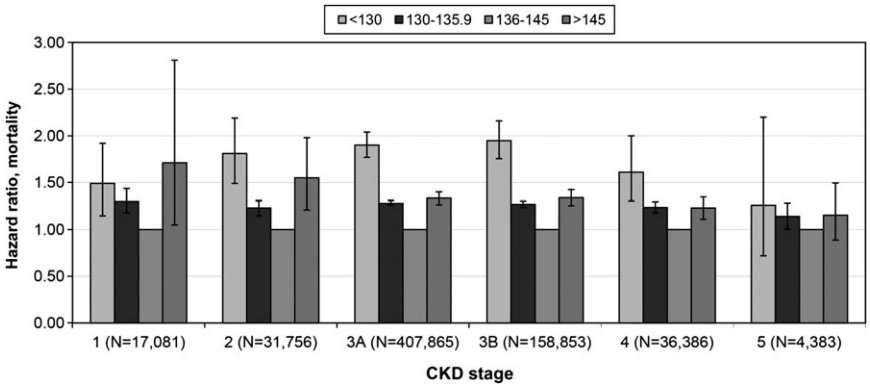

Fig. 3. Multivariable adjusted hazard ratios (95% confidence intervals) of all-cause mortality associated with mild (130–135.9 mEq/L) and moderate-to-severe (<130 mEq/L) hyponatremia and with hypernatremia (serum sodium >145 mEq/L) in 655 493 US veterans with different stages of CKD. Groups with serum sodium levels of 135–139 mEq/L served as referent. Estimates are from time-dependent Cox models adjusted for age, gender, race, geographic location, diabetes mellitus, atherosclerotic cardiovascular disease, CHF, liver disease, malignancy, depression, the Charlson comorbidity index, systolic blood pressure, eGFR, serum albumin, alkaline phosphatase, aspartate and alanine aminotransferases, total bilirubin, blood hemoglobin, glucose and white blood cell count. Results are based on data obtained from [55].

marker of increased inter-dialytic volume gain and consequently of a certain lifestyle of non-adherence with medical instructions, the need for interventional trials remains present for proof of a causal effect of hypo- and hypernatremia on mortality in CKD and end-stage renal disease.

Conclusions

Abnormalities in water homeostasis, manifested as hypo- and/or hypernatremia, are common clinical occurrences and are associated with adverse clinical outcomes. Patients with CKD can be affected by dysnatremias both because of the high prevalence of comorbidities that can result in dysnatremias in them and by the diminished ability of the failing kidneys to maintain an intact water homeostasis. Recent studies have suggested that the incidence and prevalence of dysnatremias, and especially those of hyponatremia, are substantial in patients with non-dialysis-dependent CKD and that they are associated with a significant increase in all-cause mortality. Hyponatremia appears to affect outcomes equally in patients with different stages of CKD, but hypernatremia appears to be associated with less severe outcomes in those with more advanced stages of CKD. Interventional trials are needed to establish if normalization of serum sodium levels can result in improving mortality rates in patients with CKD.

Acknowledgements. Dr Kovesdy is an employee of the US Department of Veterans Affairs. Opinions expressed in this paper are those of the author and do not necessarily represent the opinion of the US Department of Veterans Affairs.

Conflict of interest statement. None declared.

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Received for publication: 6.1.12; Accepted in revised form: 22.1.12

Clinical Nephrology, Vol. 82 – No. 6/2014 (397-401)

clinical nephrology
Neph Education

ISSN 0301-0430

DOI 10.5414/CN108014
e-pub: July 2, 2013

Hourly oral sodium chloride for the rapid and predictable treatment of hyponatremia

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Key words
osmoregulation – arginine vasopressin – hyponatremia – sodium chloride

Abstract. Hypertonic NaCl is first-line therapy for acute, severe and symptomatic hyponatremia; however, its use is often restricted to the intensive care unit (ICU). A 35-year-old female inpatient with an optic chiasm glioma and ventriculoperitoneal shunt for hydrocephalus developed acute hyponatremia (sodium 122 mEq/L) perhaps coinciding with haloperidol treatment. The sum of her urinary sodium and potassium concentrations was markedly hypertonic vis-à-vis plasma; it was inferred that serum sodium concentration would continue to fall even in the complete absence of fluid intake. Intravenous (IV) 3% NaCl was recommended; however, a city-wide public health emergency precluded her transfer to the ICU. She was treated with hourly oral NaCl tablets in a dose calculated to deliver the equivalent of 0.5 mL/kg/h of 3% NaCl with an objective of increasing the serum sodium concentration by 6 mEq/L. She experienced a graded and predictable increase in serum sodium concentration. A slight overshoot to 129 mEq/L was rapidly corrected with 0.25 l of D_5W, and she stabilized at 127 mEq/L. We conclude that hourly oral NaCl, in conjunction with careful monitoring of the serum sodium concentration, may provide an attractive alternative to IV 3% NaCl for selected patients with severe hyponatremia.

Introduction

Hyponatremia is a common electrolyte abnormality affecting 15 – 30% of hospitalized patients [1, 2]. Severe hyponatremia can be lethal; however, even modest changes in serum sodium concentration cause reversible defects in cognition and coordination [3] which can increase the risk of traumatic fracture [4, 5].

Since its first clinical application in 1938 [6], IV hypertonic (e.g., 3%) NaCl solution has been the primary therapy for severe, acute, and symptomatic hyponatremia [7, 8, 9]. Recent refinements to the use of hypertonic NaCl have focused on controlling and moderating the rate of increase in the serum sodium concentration [8]. Administration of hypertonic NaCl generally requires an intensive care unit setting [10]; an alternative approach obviating these limitations could prove attractive.

We report our results with hourly administration of oral sodium chloride tablets for the partial correction of severe acute hyponatremia in a 35-year-old woman, and propose that this approach may be appropriate for first-line therapy in selected patients with severe hyponatremia.

Case report

A 35-year-old woman presented to the emergency room with worsening of chronic abdominal pain. She had also developed progressive lower extremity edema over the prior several months and was treated with diuretics. She had been diagnosed with a glioma of the optic chiasm ~ 2 decades prior, for which she received chemotherapy and radiation. Following treatment, she developed anterior hypopituitarism, and required ventriculoperitoneal shunt for hydrocephalus. Medications (all chronic) included methadone, acetaminophen-hydrocodone, cyclobenzaprine, sumatriptan, ondansetron, divalproex sodium, gabapentin, low-dose furosemide, estrogen replacement, somatotropin, potassium chloride and vitamin D.

On examination in the emergency room, she was afebrile with a blood pressure of 96/69 mmHg, pulse of 63, and weight of 40 kg. She was cachectic and non-toxic-appearing. Mucosae were moist. Jugular venous pulsations were not observed. Cardiopulmonary

Received
February 1, 2013;
accepted in revised form
April 10, 2013

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Table 1. Laboratory data obtained at admission and at time of nephrology consultation.

Determination	Value: admission	Value: time of consultation
Serum Na^+ concentration	132 mEq/L	122 mEq/L
Serum K^+ concentration	4.4 mEq/L	4.3 mEq/L
Serum creatinine	1.2 mg/dL	0.7 mg/dL
Serum osmolality		251 mOsmol/kg H_2O
Urine osmolality		410 mOsmol/kg H_2O
Urine Na^+ concentration		138 mEq/L
Urine K^+ concentration		21 mEq/L

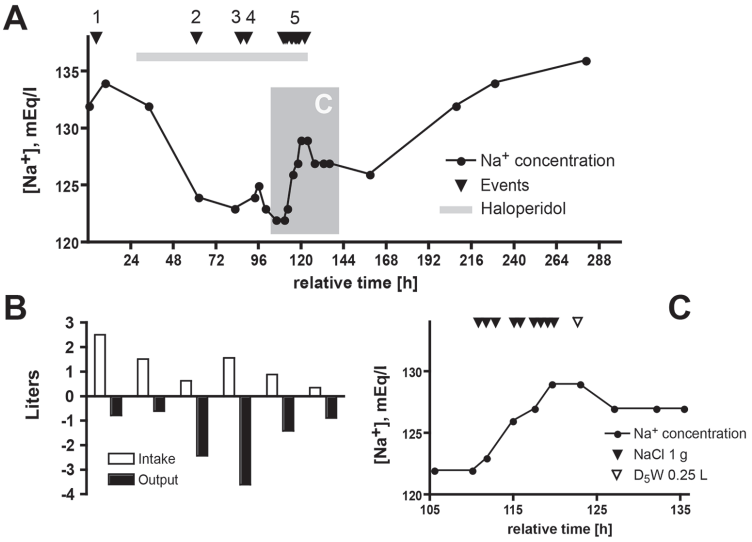

Figure 1. Data reflecting the clinical course. A: Trajectory of serum sodium concentration (mEq/L) as a function of time (in hours). Events (marked on timeline as arrowhead) are as follows: 1 – intravenous administration of 1 l normal saline; 2 – large-volume paracentesis of 3.2 l ascitic fluid; 3 – administration of 0.5 l of normal saline; 4 – imposition of 1.5 l/d fluid restriction; and 5 – treatment with oral NaCl tablets. The interval during which haloperidol was administered (total of 7 mg divided in 14 oral and parenteral doses) is marked with a horizontal gray bar. The shaded area (marked "C") is expanded in Panel C. The final four $[Na^+]$ determinations were obtained as an outpatient. B: Recorded fluid intake and urinary output (in l) in 24-hour intervals corresponding approximately to the x-axis timeline in Panel A; data for the 6th day are partial (incomplete), and data were not recorded beyond Day 6. The 24-hour intervals in B deviate by 4 hours from the interval in Panel A (time: 21:00 – 21:00 in A; 01:00 – 01:00 in B). Although not evident from the daily totals in B, much of the copious urine output on the 3rd and 4th hospital days (i.e., between hours 48 – 96) spontaneously occurred during the 8-hour overnight interval centered on Hour 72 in Panel A and totaled 2.6 l. C: Detailed trajectory of serum sodium concentration (representing shaded interval in Panel A) in response to hourly administration of NaCl (1 g tablets; filled arrowhead for each dose). Although prescribed hourly, the timing of administration was variable; depicted data reflect time of actual NaCl administration. At a serum $[Na^+]$ of 129 mEq/L, D_5W (0.25 l) was administered intravenously (open arrowhead) with a resultant decrease in serum $[Na^+]$ to 127 mEq/L.

examination was unremarkable. The abdomen was moderately distended and firm with a fluid wave. There was 1+ peripheral edema. A limited neurologic examination was without deficit.

Initial labs (Table 1) were notable for a serum sodium of 132 mEq/L (138 mEq/L 3 months prior), and a serum creatinine of 1.2 mg/dL (prior baseline 0.7 – 0.8 mg/dL). Contrast computed tomography showed new large-volume ascites. Magnetic resonance imaging of the brain showed a glioma invading the optic chiasm and the optic tract, predominantly on the left, unchanged from prior examination.

In addition to anti-emetics and narcotic analgesics, she received 1 liter of IV isotonic saline on the first hospital day. Haloperidol was begun for anxiety and in the ensuing 4 days, the patient received a total of 7 mg. By the second hospital day, renal function had returned to baseline. Serum sodium concentration decreased to 124 mEq/L on the 3rd day (Figure 1A). On transthoracic echocardiogram, there was normal left ventricular size and function. The inferior vena cava was normal in caliber with appropriate inspiratory collapse. Paracentesis was performed and she received additional isotonic saline. Urine output increased during the night of the third hospital day, to 2.6 l total for the 8-hour interval between 20:00 and 04:00 of the 4th day. On the 4th day, serum sodium concentration was 123 mEq/L and nephrology consultation was obtained.

At the time of consultation, there were no postural symptoms with ambulation. The blood pressure was 125/87, and the pulse was 66; there was no fever. Mucosae were moist and the jugular venous pressure could not be estimated. Cardiopulmonary examination was unremarkable. A small amount of ascites was present, there was no peripheral edema, and her sensorium was clear. Pertinent laboratory data are shown in Table 1. She was given a presumptive diagnosis of the syndrome of inappropriate antidiuresis based upon presumed intravascular euvolemia, multiple potentially offending medications, and the absence of urinary sodium avidity. Recommendations were to discontinue haloperidol, reduce divalproex and restrict fluids; however, in light of the substantial urine output (Figure 1B) and her urinary ($Na^+ + K^+$) far exceeding her serum ($Na^+ + K^+$), it was inferred that hyponatremia would worsen with no fluid intake. Intravenous infusion of 3% NaCl solution was recommended; however, a city-wide public health emergency (a local mass shooting) precluded ICU transfer. The sodium concentration transiently in-

creased slightly, then fell to 122 mEq/L. The duration of the public health emergency was indeterminate and, after 24 hours, the patient had still not been accepted to the ICU. Her sensorium remained clear. With a concern for possible increase in intracranial pressure, a decision was made to semi-urgently increase serum sodium concentration on the regular hospital ward with hourly NaCl tablets. An oral dosing regimen was designed to mimic a 3% NaCl infusion rate of 0.5 mL/kg/h. Her mass of 40 kg would necessitate a 20 mL/h infusion of 3% (i.e., 3 g/dL) NaCl, or 0.6 g/h of NaCl. For 1-g tablets of NaCl, this equates to 0.6 tablets per hour; this was rounded up to 1 tablet per hour in light of the urinary cation loss. (Of note, where she to have become acutely symptomatic, a more rapid rate of 3% NaCl infusion (e.g., 1 – 2 mL/kg/h) would have been targeted or used to inform the oral dosing regimen). The treatment schedule and resultant laboratory data are shown in Figure 1C. The goal was an increment in serum sodium concentration of ~ 6 mEq/L. The patient readily adhered to this regimen, and experienced a near-linear increase in serum sodium concentration. Eight hours into treatment, the serum sodium concentration was 129 mEq/L; NaCl supplementation was stopped and she received a 250 mL IV bolus of 5% dextrose in water (D_5W) with rapid stabilization of the serum sodium concentration at 127 mEq/L (Figure 1C). She was discharged on 2 gm NaCl supplementation daily. The day following discharge, her serum sodium was 126 mEq/L, and 2 days later, it had risen to 132 mEq/L, at which time NaCl supplementation was discontinued.

Discussion

To our knowledge, there are no prior reports of the use of hourly oral sodium chloride tablets for the rapid and predictable treatment of severe hyponatremia. Oral sodium chloride supplementation is commonly used after acute correction to help sustain a response to 3% NaCl solution. Alternatively, oral sodium chloride may comprise an element of a chronic outpatient maintenance regimen for the treatment of euvolemic hyponatremia [7]. Woo et al. [11] incorporated sodium chloride tablets in a prophylactic regimen for neurosurgical patients. Our inability to secure intensive care unit monitoring – owing to an unfolding city-wide public health emergency – was the basis for our formulating and implementing this strategy. We anticipate that it could prove useful for other carefully selected cases of severe hyponatremia.

A limitation of this approach is its requirement for active patient participation and adherence. Many clinical scenarios necessitating an urgent increase in the serum sodium concentration are associated with an altered sensorium; reliable adherence to an oral regimen cannot be assumed. In addition, although ICU-level care was not required to administer this regimen, intensive monitoring of the serum sodium concentration response to intervention was essential. Therefore, where nursing and/or physician manpower resources are limited, this approach may not prove advantageous. Whereas some have argued that hypertonic NaCl therapy should be reserved for the ICU [10], others routinely administer IV 3% NaCl outside of the ICU setting (e.g., [12]); the oral loading approach described here may offer fewer advantages in the latter environments.

It could be argued that urgently increasing the serum sodium concentration was not essential in this setting. Although the patient was not overtly symptomatic, the magnitude of the acute fall in serum sodium concentration was concerning and, based upon her extensive CNS pathology, we considered her particularly sensitive to the adverse effects of even mildly increased intracranial pressure. Most notably, her urinary electrolyte concentration ($Na^+ + K^+$) was hypertonic with respect to her plasma such that a progressive fall in serum sodium concentration was anticipated even in the absence of additional fluid intake. The importance of the sum of the urinary sodium and potassium concentration vis-à-vis maintenance of the serum sodium concentration formed the basis for the Edelman equation [13], and has received renewed emphasis (e.g., [9, 14, 15]). Furthermore, the distinction between the presence vs. absence of neurologic symptoms in hyponatremia is somewhat artificial [12]; most hyponatremic patients have at least subtle symptoms (e.g., [3]). For these reasons, we felt that urgent

partial correction of her serum sodium concentration was indicated.

The rate of correction remained relatively constant (Figure 1A, C). A slight overshoot occurred (1 – 2 mEq/L) and – given the negative electrolyte-free water clearance – was rapidly corrected with a modest (0.25 l) infusion of free water (D_5W). Re-lowering affords protection from adverse sequelae [16, 17, 18]. A prudent target for partial correction – in both acute and chronic hyponatremia – is an increment of 6 mEq/L within the first 24 hours. This is sufficient to prevent impending central nervous system decompensation in the acute setting [19], and to minimize the risk of myelinolysis in chronic hyponatremia [20].

A number of chronic medications could have contributed to the development of hyponatremia in this case, including narcotics [21] and valproic acid [22, 23, 24, 25]. Although most diuretic-induced hyponatremia is caused by thiazide diuretics [26], some cases are attributable to loop diuretics [27] such as furosemide in the present case.

The acute administration of haloperidol was potentially instrumental [28]. Haloperidol was prescribed as an anxiolytic for this benzodiazepine-allergic patient; its discontinuation was recommended by the consulting nephrologist but implementation was delayed. Therefore, the effective correction of the hyponatremia by supplemental oral NaCl was not confounded by cessation of haloperidol therapy. The sudden increase in urinary output – occurring principally during the night between the 3rd and 4th hospital days – would be unexpected were this to represent purely haloperidol-induced SIAD. We do not have a satisfactory explanation for the transient polyuria; it did not appear to be a water diuresis as the effect upon the serum sodium concentration was minimal at best (Figure 1A). Of note, the mild acute kidney injury had resolved by the 2nd hospital day. It seems likely that unrecorded oral intake of hypotonic fluid coincided with the development of hyponatremia during the 2nd hospital day.

A central basis for the hyponatremia was also considered. Gliomas arising from the optic chiasm have been associated with hypernatremia from central diabetes insipidus or osmoreceptor dysfunction [29]; hyponatremia/SIAD has been reported following surgery [30] and de novo in a case with features similar to the present one [31]. Abnormal adrenocortical and thyroid function can accompany pituitary failure and can give rise to an SIAD-like picture (reviewed in: [7]). This mechanism was not felt to be operative in the development of the acute inpatient hyponatremia, and her pituitary function had been closely monitored. Laboratory studies ~ 3 months prior to this admission were consistent with normal thyroid and adrenal function, and normal plasma levels of TSH and ACTH, respectively (data not shown).

Although gastrointestinal symptoms comprised the admitting complaint, and although ascites was present, there were no clinical or laboratory findings to suggest that chronic liver disease was confounding the water balance picture (data not shown). Ascites was tentatively attributed to the presence of the ventriculoperitoneal shunt (e.g., [32]). Furthermore, were cirrhosis the basis for the water avidity in the present case, an extremely low urinary sodium concentration would be expected.

The potential benefits of this hourly oral NaCl regimen include reduced cost, reduced reliance upon ICU resources, reduced need for central venous access, and a reduced number of patient care "hand-offs" obligated by team/unit transfer. In addition, this therapy can be started immediately upon recognition of hyponatremia – particularly in facilities such as our own where institutional policy precludes administration of intravenous hypertonic NaCl outside of an ICU setting. Delays are common in implementing NaCl therapy for hyponatremia [12]. Ward stocking with NaCl tablets might reduce or avoid the potential for errors in medication administration that has resulted in restricted distribution and stocking of 3% NaCl solution. We conclude that hourly oral NaCl supplementation – in conjunction with careful monitoring of the serum sodium concentration – may provide safe and effective therapy in selected patients with severe hyponatremia, and that this approach affords potential advantages over existing regimens.

Acknowledgments

This work is supported by grants from the National Institutes of Health, the Depart-

ment of Veterans Affairs, and the American Heart Association. The authors have no conflict of interest related to the contents of this manuscript.

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High and low sodium intakes are associated with incident chronic kidney disease in patients with normal renal function and hypertension

see commentary on page 776

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The association between salt intake and renal outcome in subjects with preserved kidney function remains unclear. Here we evaluated the effect of sodium intake on the development of chronic kidney disease (CKD) in a prospective cohort of people with normal renal function. Data were obtained from the Korean Genome and Epidemiology Study, a prospective community-based cohort study while sodium intake was estimated by a 24-hour dietary recall Food Frequency Questionnaire. A total of 3,106 individuals with and 4,871 patients without hypertension were analyzed with a primary end point of CKD development [a composite of estimated glomerular filtration rate (eGFR) under 60 mL/min/1.73 m^2 and/or development of proteinuria during follow-up]. The median ages were 55 and 47 years, the proportions of males 50.9% and 46.3%, and the median eGFR 92 and 96 mL/min/1.73 m^2 in individuals with and without hypertension, respectively. During a median follow-up of 123 months in individuals with hypertension and 140 months in those without hypertension, CKD developed in 27.8% and 16.5%, respectively. After adjusting for confounders, multiple Cox models indicated that the risk of CKD development was significantly higher in people with hypertension who consumed less than 2.08 g/day or over 4.03 g/day sodium than in those who consumed between 2.93–4.03 g/day sodium. However, there was no significant difference in the incident CKD risk among each quartile of people without hypertension. Thus, both high and low sodium intakes were associated with increased risk for CKD, but this relationship was only observed in people with hypertension.

Kidney International (2018) **93,** 921–931; https://doi.org/10.1016/j.kint.2017.09.016

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Received 17 February 2017; revised 17 September 2017; accepted 21 September 2017; published online 29 November 2017

KEYWORDS: chronic kidney disease; dietary sodium; hypertension

Chronic kidney disease (CKD) is a major risk factor for cardiovascular disease and death.[1,2] Blood glucose control and hypertension management are strategies that have been applied to prevent the development and progression of CKD. Nonetheless, the prevalence of CKD is rapidly increasing worldwide. Because established CKD is an irrecoverable condition, identifying modifiable factors and applying early interventions are crucial for reducing the burden of CKD.

Dietary sodium intake has been repeatedly reported to have an influence on cardiovascular risk factors and outcomes in several patient groups. A high sodium diet is known to aggravate hypertension,[3–5] and studies have shown high sodium intake to be also associated with an increased incidence of cardiovascular diseases.[6–13] However, restriction in dietary sodium intake also activates the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system.[14–16] Aggravation of insulin resistance has also been reported in subjects consuming low dietary sodium.[17] Accordingly, a recent investigation showed that survival of patients with type 1 diabetes can be reduced not only by high urinary sodium excretion but also low excretion.[13]

As hypertension is a major risk factor for CKD,[18] the clear connection between sodium intake and blood pressure also links dietary sodium to CKD.[19–21] However, its association with renal function is less well investigated and confounding. Although several studies have shown that high dietary sodium intake increases the risk of CKD development or progression,[13,22–25] some results failed to find significant connections to renal outcome.[22,26–30] In addition, although the adverse effects of increased dietary sodium on cardiovascular outcomes are more prominent in subjects with hypertension than in those without,[4,8,9] influence of hypertension on the relationship between sodium intake and CKD development is not known.

Therefore, in order to investigate whether dietary sodium intake affects CKD development, this study assessed a prospective community-based cohort of subjects with normal renal function with and without hypertension.

RESULTS

Baseline characteristics

The baseline characteristics of subjects with and without hypertension are shown in Tables 1 and 2, respectively. The median (range) of the subjects' ages were 55 (47–63) and 47 (43–56) years; the numbers of male subjects were 1581 (50.9%) and 2255 (46.3%); and the median (range) of estimated glomerular filtration rates (eGFRs) were 92 (81–100) and 96 (84–105) ml/min per 1.73 m^2 in subjects with and without hypertension, respectively. The average (range) dietary intake of sodium were 2.93 g (2.08 g–4.03 g) in subjects with hypertension and 2.93 g (2.09 g–3.95 g) in subjects without hypertension.

Stratification into quartiles was done according to the amount of dietary sodium intake for subjects with and without hypertension. The proportions of participants with diabetes did not differ, and eGFRs were comparable in each quartile group with and without hypertension. When comparisons were made among the dietary sodium intake quartile groups of subjects with and without hypertension, participants in the higher sodium intake groups tended to

Table 1 | Baseline characteristics of subjects with hypertension

		Quartiles of dietary sodium intake (g/d)				
Variables[a]	Total (*N* = 3106)	Q1 (*N* = 777) <2.08	Q2 (*N* = 776) 2.08–2.93	Q3 (*N* = 777) 2.93–4.03	Q4 (*N* = 776) >4.03	*P*
Dietary composition						
Na intake (g/d)	2.93 (2.08, 4.03)	1.56 (1.20, 1.82)	2.53 (2.32, 2.74)	3.40 (3.14, 3.67)	5.02 (4.44, 6.05)	<0.001
Demographic data						
Age (yr)	55 (47, 63)	57 (49, 64)	55 (47, 63)	54 (46, 62)	55 (46, 62)	<0.001
Male (%)	1581 (50.9)	295 (38.0)	382 (49.2)	444 (57.1)	460 (59.3)	<0.001
SBP (mm Hg)	134 (126, 146)	136 (126, 148)	134 (126, 146)	134 (126, 144)	134 (126, 146)	0.17
DBP (mm Hg)	90 (84, 96)	90 (84, 94)	90 (84, 96)	90 (84, 96)	90 (84, 98)	0.07
BMI (kg/m^2)	25.4 (23.2, 27.4)	25.0 (22.8, 27.3)	25.5 (23.4, 27.5)	25.5 (23.4, 27.3)	25.5 (23.5, 27.4)	0.04
Waist-to-hip ratio	0.92 (0.87, 0.96)	0.92 (0.87, 0.97)	0.91 (0.86, 0.96)	0.91 (0.86, 0.96)	0.92 (0.88, 0.96)	0.01
Education (%)						<0.001
Low	1310 (42.5)	397 (51.8)	323 (41.7)	291 (37.6)	299 (38.9)	
Intermediate	675 (21.9)	160 (20.9)	181 (23.4)	158 (20.4)	176 (22.9)	
High	1098 (35.6)	210 (27.4)	270 (34.9)	324 (41.9)	294 (38.2)	
Income (%)						<0.001
Low	1325 (43.3)	401 (52.1)	320 (41.9)	287 (37.5)	317 (41.5)	
Intermediate	847 (27.7)	208 (27.0)	223 (29.2)	203 (26.5)	213 (27.9)	
High	890 (29.1)	161 (20.9)	221 (28.9)	275 (35.9)	233 (30.5)	
Married (yes)	2750 (88.9)	659 (84.8)	688 (88.9)	701 (90.6)	702 (91.3)	<0.001
Ever drink (%)	1695 (54.8)	351 (45.4)	427 (55.2)	456 (58.8)	461 (59.6)	<0.001
Ever smoke (%)	1310 (42.5)	249 (32.4)	307 (39.8)	354 (45.9)	400 (52.1)	<0.001
Exercise (MET, k)	8.8 (4.8, 16.4)	8.0 (4.4, 16.4)	8.5 (4.9, 16.1)	8.8 (5.0, 15.9)	10.0 (5.4, 17.1)	<0.001
Comorbidities (%)						
Diabetes	598 (19.3)	157 (20.2)	145 (18.7)	166 (21.4)	130 (16.8)	0.11
Dyslipidemia	97 (3.1)	22 (2.8)	24 (3.1)	30 (3.9)	21 (2.7)	0.56
CVD[b]	130 (4.2)	40 (5.1)	37 (4.8)	26 (3.3)	27 (3.5)	0.19
Laboratory parameters[c]						
Na (mmol/l)	143 (142, 144)	143 (141, 144)	143 (141, 144)	143 (142, 144)	143 (142, 144)	0.49
BUN (mg/dl)	14.1 (11.9, 16.7)	14.1 (11.7, 16.5)	14.1 (11.9, 16.7)	14.0 (11.8, 16.6)	14.2 (12.0, 16.9)	0.35
Creatinine (mg/dl)	0.8 (0.7, 1.0)	0.8 (0.7, 0.9)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	<0.001
eGFR (ml/min per 1.73 m^2)	92 (81, 100)	93 (81, 100)	92 (81, 101)	92 (80, 100)	93 (81, 101)	0.72
Hemoglobin (g/dl)	13.8 (12.7, 14.9)	13.4 (12.5, 14.6)	13.9 (12.8, 14.9)	14.0 (12.8, 15.1)	14.0 (12.9, 15.1)	<0.001
Glucose (mg/dl)	84 (79, 93)	83 (77, 92)	84 (79, 92)	86 (80, 95)	85 (79, 93)	0.001
HbA1c (%)	5.7 (5.4, 6.0)	5.7 (5.4, 6.0)	5.7 (5.4, 6.0)	5.7 (5.4, 6.1)	5.7 (5.4, 6.0)	0.86
Albumin (g/dl)	4.2 (4.1, 4.4)	4.2 (4.1, 4.4)	4.2 (4.1, 4.4)	4.2 (4.1, 4.5)	4.2 (4.1, 4.4)	0.08
Cholesterol (mg/dl)	193 (171, 218)	192 (170, 217)	193 (170, 217)	197 (173, 223)	190 (170, 215)	0.79
Triglyceride (mg/dl)	153 (112, 212)	146 (109, 199)	152 (111, 204)	159 (113, 228)	156 (115, 223)	<0.001
HDL-C (mg/dl)	43 (37, 49)	43 (37, 49)	43 (37, 50)	43 (37, 49)	43 (37, 49)	0.91
LDL-C (mg/dl)	115 (93, 137)	116 (93, 138)	115 (94, 139)	118 (95, 139)	111 (90, 134)	0.03
CRP (mg/l)	0.16 (0.08, 0.27)	0.16 (0.08, 0.26)	0.15 (0.08, 0.26)	0.17 (0.08, 0.31)	0.16 (0.08, 0.27)	0.66

BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; Na, sodium; Q, quartile; SBP, systolic blood pressure.

[a]All continuous variables are expressed as median (25th, 75th percentiles). The values expressed as mean and SD can be found in Supplementary Table S1.

[b]A history of cardiovascular disease was defined as the composite of myocardial infarction, congestive heart failure, coronary artery disease, peripheral artery disease, and/or cerebrovascular accident.

[c]*P* for trend was conducted by using the Jonckheere-Terpstra test.

Table 2 | Baseline characteristics of subjects without hypertension

Variables[a]	Total (N = 4871)	Quartiles of dietary sodium intake (g/d)				P
		Q1 (N = 1218), <2.09	Q2 (N = 1218), 2.09–2.94	Q3 (N = 1218), 2.94–3.95	Q4 (N = 1217), >3.95	
Dietary composition						
Na intake (g/d)	2.93 (2.09, 3.95)	1.58 (1.25, 1.83)	2.54 (2.32, 2.74)	3.36 (3.14, 3.64)	4.83 (4.31, 5.87)	<0.001
Demographic data						
Age (yr)	47 (43, 56)	48 (43, 58)	47 (43, 56)	47 (43, 55)	48 (43, 57)	<0.001
Male (%)	2255 (46.3)	478 (39.2)	524 (43.0)	597 (49.0)	656 (53.9)	<0.001
SBP (mm Hg)	110 (102, 118)	110 (102, 120)	110 (102, 118)	110 (100, 118)	110 (102, 120)	0.02
DBP (mm Hg)	74 (70, 80)	74 (70, 80)	74 (70, 80)	72 (68, 80)	74 (70, 80)	0.06
BMI (kg/m^2)	23.9 (22.1, 25.9)	23.8 (22.1, 25.8)	23.9 (22.1, 25.7)	24.2 (22.1, 26.0)	24.0 (22.1, 26.0)	0.16
Waist-to-hip ratio	0.87 (0.81, 0.92)	0.87 (0.81, 0.93)	0.86 (0.80, 0.91)	0.86 (0.81, 0.91)	0.88 (0.83, 0.92)	<0.001
Education (%)						0.008
Low	1282 (26.4)	366 (30.2)	321 (26.5)	289 (23.8)	306 (25.2)	
Intermediate	1121 (23.1)	281 (23.2)	263 (21.7)	286 (23.6)	291 (24.0)	
High	2446 (50.4)	563 (46.5)	629 (51.9)	638 (52.6)	616 (50.8)	
Income (%)						<0.001
Low	1364 (28.4)	414 (34.7)	312 (25.8)	297 (24.5)	341 (28.6)	
Intermediate	1468 (30.6)	356 (29.8)	382 (31.6)	368 (30.4)	362 (30.4)	
High	1971 (41.0)	423 (35.5)	514 (42.5)	545 (45.0)	489 (41.0)	
Married (yes)	4454 (91.8)	1100 (90.6)	1106 (91.0)	1127 (92.9)	1121 (92.5)	0.11
Ever drink (%)	2609 (53.8)	586 (48.2)	630 (51.8)	687 (56.6)	706 (58.4)	<0.001
Ever smoke (%)	1956 (40.5)	426 (35.2)	446 (36.8)	510 (42.2)	574 (47.6)	<0.001
Exercise (MET, k)	7.9 (4.8, 13.4)	7.6 (4.7, 13.3)	7.9 (4.7, 11.9)	8.0 (5.3, 13.0)	8.5 (5.0, 15.5)	<0.001
Comorbidities (%)						
Diabetes	480 (9.9)	113 (9.3)	115 (9.4)	117 (9.6)	135 (11.1)	0.41
Dyslipidemia	94 (1.9)	22 (1.8)	28 (2.3)	21 (1.7)	23 (1.9)	0.74
CVD[b]	87 (1.8)	22 (1.8)	16 (1.3)	24 (2.0)	25 (2.1)	0.52
Laboratory parameters[c]						
Na (mmol/l)	143 (141, 144)	143 (141, 144)	143 (141, 144)	143 (141, 144)	142 (141, 144)	0.10
BUN (mg/dl)	13.7 (11.6, 16.1)	13.5 (11.5, 16.0)	13.7 (11.5, 16.0)	13.6 (11.6, 16.0)	14.0 (11.8, 16.5)	0.002
Creatinine (mg/dl)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	<0.001
eGFR (ml/min per 1.73 m^2)	96 (84, 105)	97 (84, 105)	97 (86, 105)	96 (84, 105)	96 (84, 105)	0.44
Hemoglobin (g/dl)	13.4 (12.4, 14.6)	13.2 (12.3, 14.4)	13.4 (12.5, 14.5)	13.5 (12.5, 14.7)	13.7 (12.6, 14.8)	<0.001
Glucose (mg/dl)	82 (77, 88)	81 (76, 87)	82 (77, 88)	82 (77, 88)	82 (77, 90)	0.001
HbA1c (%)	5.5 (5.3, 5.8)	5.5 (5.3, 5.8)	5.5 (5.3, 5.8)	5.5 (5.3, 5.8)	5.6 (5.3, 5.9)	0.17
Albumin (g/dl)	4.2 (4.0, 4.4)	4.1 (4.0, 4.4)	4.2 (4.1, 4.4)	4.2 (4.1, 4.4)	4.1 (4.0, 4.4)	0.11
Cholesterol (mg/dl)	186 (165, 209)	183 (163, 208)	187 (164, 211)	187 (165, 210)	186 (166, 210)	0.05
Triglyceride (mg/dl)	124 (94, 172)	122 (92, 170)	124 (94, 171)	122 (92, 171)	129 (96, 176)	0.04
HDL-C (mg/dl)	44 (38, 50)	44 (38, 51)	44 (38, 51)	44 (38, 50)	44 (38, 50)	0.79
LDL-C (mg/dl)	112 (93, 134)	111 (91, 132)	113 (94, 135)	113 (94, 133)	112 (92, 135)	0.27
CRP (mg/l)	0.13 (0.06, 0.22)	0.13 (0.06, 0.22)	0.13 (0.06, 0.22)	0.13 (0.06, 0.23)	0.13 (0.05, 0.23)	0.81

BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; Na, sodium; Q, quartile; SBP, systolic blood pressure.
[a]All continuous variables are expressed as median and 25th and 75th percentiles. The values expressed as mean and SD can be found in Supplementary Table S2.
[b]A history of CVD was defined as the composite of myocardial infarction, congestive heart failure, coronary artery disease, peripheral artery disease, and/or cerebrovascular accident.
[c]P for trend was conducted by using the Jonckheere-Terpstra test.

be younger, male, to be more educated, to have a higher income, and to have a higher body mass index and waist-to-hip ratio. In addition, subjects with and without hypertension in the higher sodium intake groups more frequently had a history of smoking or drinking and were more physically active. Laboratory data assessment of subjects with hypertension revealed that creatinine, hemoglobin, glucose, and triglyceride levels tended to higher in subjects with higher dietary sodium intake. As for subjects without hypertension, the levels of blood urea nitrogen, creatinine, hemoglobin, glucose, total cholesterol, and triglyceride tended to increase in those with higher dietary sodium intake.

The total calorie, protein, fat, carbohydrate, and potassium intakes were significantly increased with higher sodium intake regardless of hypertension status (Figure 1).

Development of incident CKD

During a median (range) follow-up duration of 122.8 (68.9–143.0) months in subjects with hypertension and 140.0 (95.4–143.1) months in those without hypertension, CKD developed in 864 (27.8%) and 803 (16.5%) subjects, respectively.

Impact of dietary sodium intake on incident CKD

The Kaplan-Meier plots constructed for subjects with hypertension showed that the time to the development of

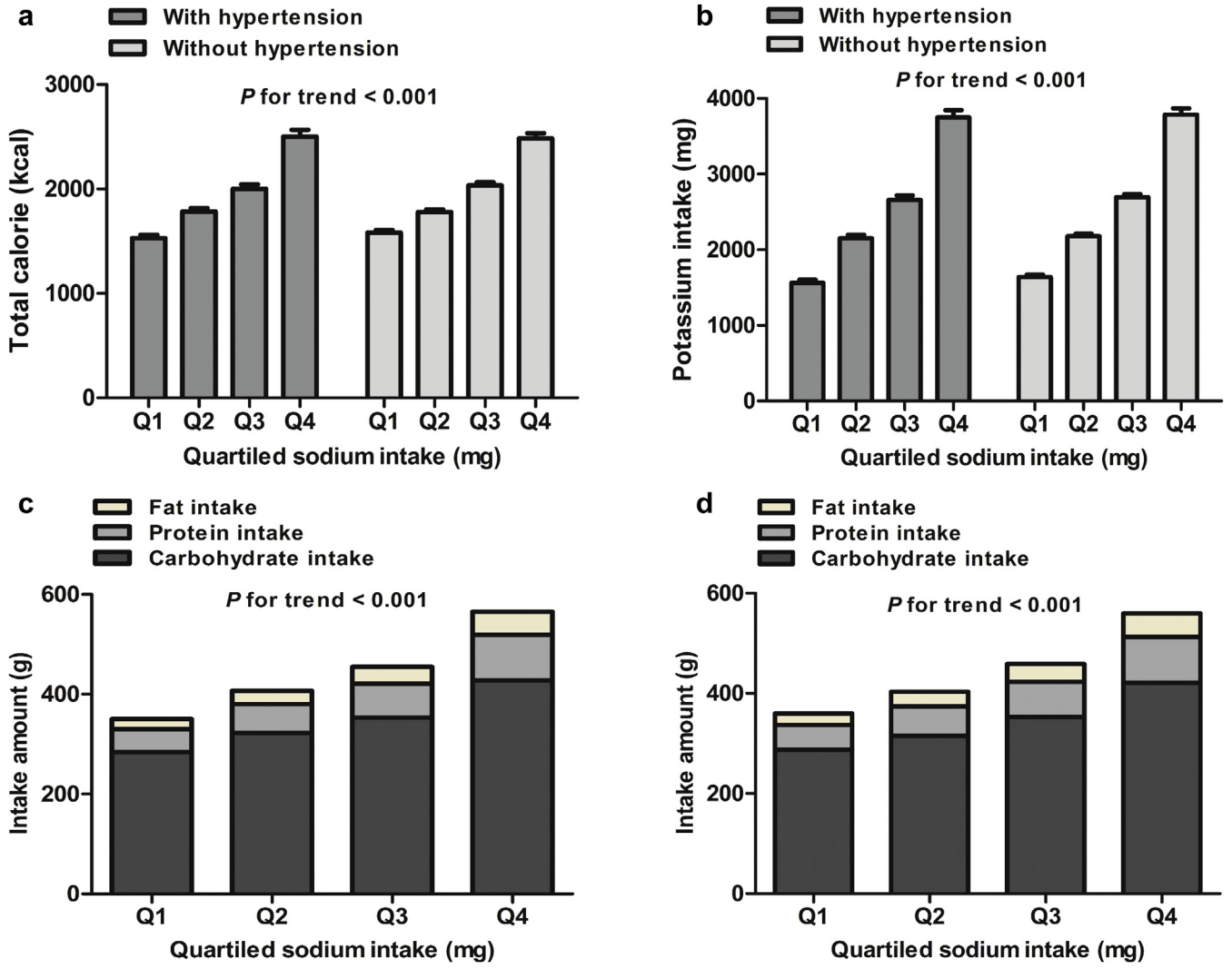

Figure 1 | Comparisons of dietary components according to quartiles of dietary sodium intake. Total calorie (**a**) is increased in parallel with increased amounts of dietary sodium intake in subjects with hypertension (*P* for trend <0.001) and those without hypertension (*P* for trend <0.001). Potassium intake shows similar trend of total calorie intake in both groups (**b**; *P* for trend <0.001). Fat, protein, and carbohydrate intakes increase according to greater intake of dietary sodium in subjects with hypertension (**c**; *P* for trend; fat, protein, and carbohydrate 0.620, 0.039, and <0.001) and those without hypertension (**d**; *P* for trend; fat, protein, and carbohydrate; <0.001, <0.001, and <0.001).

incident CKD was significantly longer in those consuming 2.93 to 4.03 g/d sodium (quartile [Q]3) than in those with-dietary sodium intake <2.08 g/d (Q1, $P < 0.001$) (Figure 2a). However, a significant difference was not found among subjects assigned to each quartile in those without hypertension (Figure 2b).

Multiple Cox proportional hazard regression models revealed that the risk of CKD development was significantly higher in subjects with dietary sodium intake <2.08 g/d (Q1: hazard ratio [HR], 1.35; 95% confidence interval [CI] 1.09–1.68; $P = 0.007$) and >4.03 g/d (Q4: HR, 1.38; 95% CI 1.10–1.73; $P = 0.005$) than in those who consumed 2.93 to 4.03 g/d sodium (Q3) among subjects with hypertension after adjusting for confounding variables. This significant increase in CKD risk was robust even when adjustments were made for the best fit model (Q1: HR, 1.32; 95% CI 1.08–1.61; $P = 0.008$; Q4: HR, 1.28; 95% CI 1.04–1.58; $P = 0.02$). However, there was no significant difference in the incident CKD risk among each quartile group of subjects without hypertension (Table 3).

The relationship between dietary sodium intake and incident CKD was further investigated in subgroups stratified by age, sex, and body mass index. Consuming <2.08 g/d (Q1: HR, 1.60; 95% CI 1.13–2.27; $P = 0.008$) or >4.03 g/d (Q4: HR, 1.86; 95% CI 1.33–2.60; $P < 0.001$) sodium significantly increased the risk of CKD development in subjects with hypertension younger than 60 years of age compared with those in the reference sodium intake quartile group (Q3). This significant relationship was also found in female subjects with hypertension (Q1: HR, 1.49; 95% CI 1.11–2.00; $P = 0.009$; Q4: HR, 1.74; 95% CI 1.26–2.41; $P = 0.001$). This relationship was significant regardless of body mass index (Table 4, Figure 3).

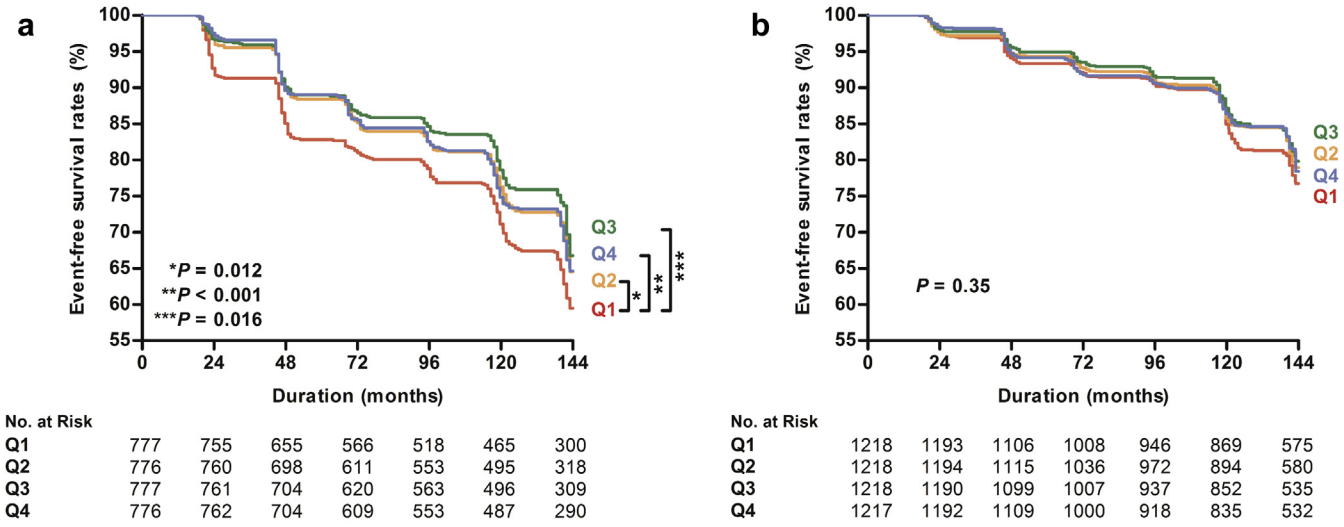

Figure 2 | Kaplan-Meier plot and incident CKD development according to dietary sodium intake in subjects with (a) and without (b) hypertension. *$P < 0.012$; **$P < 0.001$; ***$P = 0.016$. CKD, chronic kidney disease.

DISCUSSION

In this study, the relationship between dietary sodium intake and development of CKD was investigated in subjects with normal kidney function. Both high and low dietary sodium intake significantly increased the risk of CKD compared with moderate sodium intake in subjects with hypertension. However, the amount of sodium intake did not affect incident CKD development in subjects without hypertension. These findings suggest that a well-balanced dietary sodium intake is helpful in preserving renal function and that this effect is dependent on blood pressure status.

The relationship between dietary sodium intake and CKD development in this study was modified by hypertension status. This finding is in line with the results of recently published studies on the relationship of dietary sodium intake with cardiovascular disease. A prospective cohort study of 7543 subjects reported that the association between high sodium intake and coronary heart disease was confined to patients with hypertension or with increased concentrations of amino-terminal pro-brain natriuretic peptide.[8] In addition, a pooled analysis of 4 prospective studies showed an association between increased salt intake and cardiovascular events only in subjects with hypertension.[9] Although the modifying effect of hypertension status on the relationship between sodium intake and renal outcome has not been reported previously, a similar effect could be analogized from previous studies. High urinary sodium excretion was found to be associated with increased risk of CKD progression in patients with prevalent CKD in the Chronic Renal Insufficiency Cohort (CRIC) study.[23] However, the amount of urinary

Table 3 | Multivariate Cox proportional hazards regression analyses of association between dietary sodium intake and incident CKD

		Dietary sodium intake (versus Q3)						
		Q1		Q2			Q4	
	Models	HR (95% CI)	P	HR (95% CI)	P	Q3	HR (95% CI)	P
With hypertension	1	1.31 (1.08–1.58)	0.005	1.10 (0.90–1.34)	0.34	1.0 (reference)	1.20 (0.99–1.47)	0.06
	2	1.32 (1.07–1.63)	0.009	1.16 (0.94–1.43)	0.17		1.38 (1.11–1.71)	0.004
	3[a]	1.34 (1.08–1.67)	0.009	1.19 (0.96–1.46)	0.11		1.40 (1.11–1.75)	0.004
	Plus BMI[a]	1.35 (1.09–1.68)	0.007	1.18 (0.95–1.46)	0.13		1.38 (1.10–1.73)	0.005
	Best fit model[b]	1.32 (1.08–1.61)	0.008	1.12 (0.92–1.37)	0.25		1.28 (1.04–1.58)	0.02
Without hypertension	Model 1	1.04 (0.86–1.27)	0.70	1.05 (0.86–1.28)	0.66		1.01 (0.82–1.23)	0.94
	Model 2	1.05 (0.85–1.30)	0.66	1.09 (0.89–1.35)	0.40		0.97 (0.78–1.21)	0.80
	Model 3	1.05 (0.84–1.31)	0.67	1.09 (0.88–1.34)	0.44		0.95 (0.75–1.19)	0.65
	Plus BMI	1.05 (0.84–1.31)	0.66	1.09 (0.88–1.34)	0.44		0.95 (0.75–1.19)	0.64
	Best fit model[c]	1.06 (0.86–1.30)	0.59	1.06 (0.87–1.30)	0.56		0.97 (0.78–1.19)	0.75

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; Q, quartile.
Model 1: Adjusted for age, sex, and estimated glomerular filtration rate.
Model 2: Model 1 + protein intake, fat intake, waist-to-hip ratio, education, income, diabetes, cardiovascular disease, serum sodium, fasting glucose, and triglyceride.
Model 3: Model 2 + potassium intake, systolic blood pressure, marital status, smoking, exercise, hemoglobin, and serum albumin.
[a]Adjusted with spline term of systolic blood pressure.
[b]Adjusted for age, sex, estimated glomerular filtration rate, protein intake, fat intake, education, income, diabetes, triglyceride, exercise, and serum albumin.
[c]Adjusted for age, sex, estimated glomerular filtration rate, income, fasting glucose, triglyceride, and serum albumin.

Table 4 | Subgroup analyses of the relationship between dietary sodium intake and incident CKD

Variables		Hazard ratio (95% confidence interval)						
		Q1	*P*	Q2	*P*	Q3	Q4	*P*
With hypertension	Age <60 yr[a]	1.60 (1.13–2.27)	0.008	1.20 (0.86–1.67)	0.29	Reference	1.86 (1.33–2.60)	<0.001
	Age ≥60 yr	1.18 (0.88–1.57)	0.27	1.11 (0.84–1.46)	0.47		1.08 (0.78–1.48)	0.65
	Male[a]	1.15 (0.81–1.61)	0.44	1.01 (0.74–1.37)	0.96		1.08 (0.78–1.49)	0.64
	Female	1.49 (1.11–2.00)	0.009	1.33 (0.99–1.80)	0.06		1.74 (1.26–2.41)	0.001
	BMI <25.0 kg/m^2	1.41 (1.01–1.97)	0.046	1.23 (0.88–1.72)	0.22		1.44 (1.00–2.09)	0.05
	BMI ≥25.0 kg/m^2[a]	1.37 (1.02–1.83)	0.04	1.14 (0.87–1.51)	0.35		1.36 (1.02–1.80)	0.04
Without hypertension	Age <60 yr	1.19 (0.90–1.58)	0.22	1.22 (0.94–1.60)	0.14		0.91 (0.68–1.22)	0.53
	Age ≥60 yr	0.88 (0.61–1.28)	0.51	0.93 (0.65–1.32)	0.68		0.99 (0.68–1.44)	0.96
	Male	1.14 (0.78–1.65)	0.50	1.32 (0.95–1.83)	0.10		1.02 (0.72–1.43)	0.93
	Female	1.01 (0.76–1.33)	0.96	0.94 (0.71–1.24)	0.66		0.92 (0.67–1.26)	0.61
	BMI <25.0 kg/m^2	1.17 (0.88–1.55)	0.28	1.15 (0.88–1.50)	0.32		1.00 (0.74–1.34)	0.98
	BMI ≥25.0 kg/m^2	0.92 (0.63–1.34)	0.67	1.04 (0.73–1.47)	0.85		0.90 (0.62–1.29)	0.56

BMI, body mass index; CKD, chronic kidney disease; Q, quartile.
Adjustments were made for age, sex, estimated glomerular filtration rate, protein intake, fat intake, waist-to-hip ratio, education, income, diabetes, cardiovascular disease, serum sodium, fasting glucose, triglyceride, potassium intake, systolic blood pressure, marital status, smoking, exercise, hemoglobin, serum albumin, and BMI.
[a]Adjusted with spline term of systolic blood pressure.

sodium excretion did not increase the risk of CKD development in a cohort with normal kidney function enrolled in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study.[27] Considering that 85% of participants in the CRIC study were hypertensive, whereas only 10% of subjects in the PREVEND study had hypertension, there is a possibility that hypertension status could have played a role in the different effects of sodium intake on renal function decline.

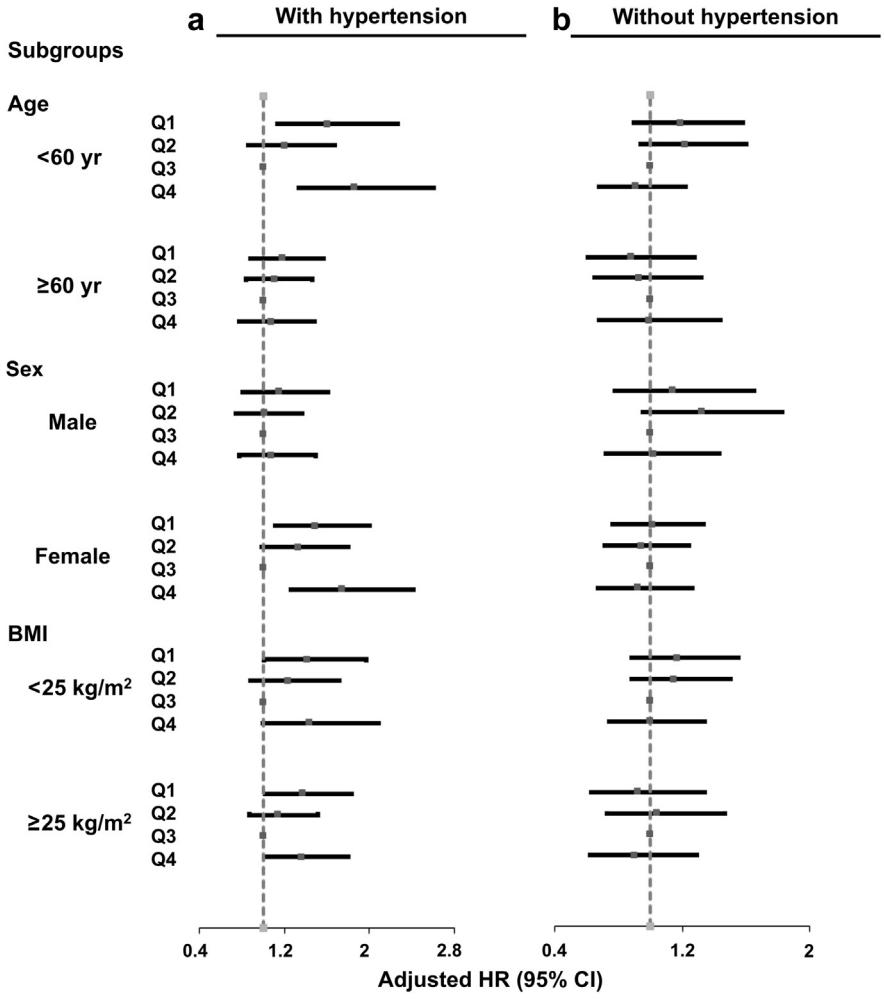

Figure 3 | Forest plots for subgroup analyses of incident chronic kidney disease development according to dietary sodium intake in subjects with (a) and without (b) hypertension. BMI, body mass index; CI, confidence interval; HR, hazard ratio; Q, quartile.

One reason for this modification effect by hypertension status might be related to salt sensitivity. Adverse effects of high salt intake are known to be evident in increasing blood pressure.[3–5] Randomized trials have shown that the blood pressure–lowering effect of decreased salt intake is limited in subjects without hypertension,[31] suggesting that blood pressure in such subjects may be less sensitive to salt intake. Another possibility is that adverse renal outcomes could have worsened in subjects with hypertension. Because hypertension is a major risk factor for CKD development,[18] target organ damage would have been aggravated by the concomitant effect of hypertension and dietary sodium.

Adverse effects of increased sodium intake on target organs are thought to be linked to blood pressure elevation. However, blood pressure did not differ among the quartile groups of dietary sodium intake. This could be due to the fact that most of the subjects with hypertension received antihypertensive treatment, and their blood pressure was mostly well controlled. Nonetheless, sodium intake was found to play a role in CKD development, which was a noticeable result even after adjusting for confounding variables, including blood pressure. Therefore, there is a possibility that dietary sodium might have affected renal function, regardless of its influence on blood pressure. Several possible mechanisms could be speculated from animal studies. High dietary sodium increases oxidative stress by decreasing the renal expression of superoxide dismutase in rats.[32] In addition, sodium intake is known to modulate renal transforming growth factor-β and nitric oxide by having direct effects on the endothelium.[33] Moreover, studies have shown that dietary sodium also influences insulin resistance and metabolic syndrome, raising the possibility that effects on metabolism could also play a role in renal function decline.[17,34]

Interestingly, not only higher dietary sodium intake but also low sodium intake increased the risk of CKD development. Sodium is a cation that is essential for maintaining cellular function, and its balance is tightly regulated through various physiological mechanisms. Given the inherent features of the sodium-based mechanism underlying the maintenance of cellular homeostasis of the human body, extreme limitation of sodium intake may not be beneficial in the long term.[35,36] Some experimental or clinical studies can provide evidence for this assumption. For example, dietary sodium restriction exacerbated atherosclerosis in apolipoprotein E–deficient mice.[37] In addition, dietary sodium restriction in combination with angiotensin-converting enzyme inhibition resulted in aggravation of tubulointerstitial damage in healthy rats.[38] Moreover, observational studies have found that low sodium intake activates the RAAS and catecholamines,[39] all of which are known to affect renal function. Similarly, adverse effects of sodium intake have been also noted in patients with cardiovascular diseases.[10] When sodium intake was estimated by using urinary sodium excretion measurements, an estimated sodium intake of 3 to 6 g/d was associated with a lower risk of death and cardiovascular events than was a higher or lower level of intake. Concerning renal outcome, an investigation of patients with type 1 diabetes with prevalent CKD showed that a low amount sodium intake was associated with higher risks of CKD progression.[13] However, this study is the first to suggest the possibility that low sodium intake could exacerbate renal function decline even in the general population.

There is a possibility that the increased risk of CKD development found with low sodium intake could have been a result of the concomitant conditions compromising nutritional status. However, the prevalence of comorbidities such as diabetes and cardiovascular diseases did not differ among the quartile groups of dietary sodium intake. In addition, the effect of dietary sodium on renal outcome was significant even after adjustments for comorbidities, lowering the chances of low sodium intake being a consequence of deteriorated nutritional status. Nonetheless, the adverse renal outcome found in subjects with low salt intake could have resulted from the effect of other nutrients, which is plausible because the intake of nutrients such as potassium, fat, protein, and carbohydrate differed in proportion to the intake of sodium. In particular, low potassium intake could have influenced renal function, taking into account the results of recent investigations showing that low potassium intake significantly increases the risk of both cardiovascular disease and renal function decline.[10,11,23,27,29,30,40] Nevertheless, it should be noted that the increase in CKD risk with low sodium intake was significant even after adjusting for these nutrients. The chance of reverse causation by intentionally restricting sodium intake in high-risk patients should also be considered. However, the fact that comorbid conditions or factors known to increase the risk of CKD did not differ among the different sodium intake groups lowers such possibility.

The average daily sodium intake in South Korea is higher than those in most Western countries. In a study that estimated the sodium intake in a representative adult population through sodium measurements in 24-hour urine collection samples, the average sodium intake in South Korea was 4.18 g/d for men and 3.48 g/d for women.[41] In order to assess whether incident CKD risk differs with the amount of sodium intake relative to the average amount of consumption, sodium intake quartile groups with and without hypertension, which included the average South Korean sodium intake, were chosen as reference groups in regression analyses. Therefore, the results of this study may indicate that the risk of renal function deterioration could be higher in hypertensive subjects who consume more sodium than the average population. Sodium intake amount in South Korea has been gradually decreasing due to changes in diet patterns and increased health concerns. Therefore, future investigations should be conducted to evaluate whether a change in the average amount of sodium consumption has an impact on the relationship between incident CKD risk and sodium intake.

The Korean Genome and Epidemiology Study (KoGES) cohort used in this study was designed to include subjects from both rural and urban areas in South Korea, for a better

representation of the general South Korean population. The age-standardized prevalence rates of diabetes and obesity in the KoGES cohort were comparable to those of another large-scale national cohort known as the Korea National Health and Nutrition Examination Survey (KNHANES), although the prevalence of hypertension appeared to be somewhat higher in the KoGES group (33.9% vs. 28.0%).[42,43] In addition, the mortality rate and the number of incident cancer cases were also comparable between the 2 cohorts. Comparisons of patient characteristics and health outcomes using KNHANES offer supportive evidence that KoGES data can be generalized for the entire South Korean population.[42]

Some limitations of this study must be addressed. First, limitations of observational cohort studies were inevitable. Although a sequential relationship was found between sodium intake and CKD development, statistical independence of effects does not imply strict causality. Randomized controlled trials are needed to further clarify the association found in this study. Second, sodium intake was estimated by dietary intake ascertained from a 24-hour dietary recall Food Frequency Questionnaire (FFQ). Although dietary recall lacks precision compared with measurements of urinary sodium excretion, performance of the 2 measurement modes is rather similar regardless of demographic subgroups.[44] In addition, this method provides a measure of diet intake feasible for large-scale studies. Moreover, both the validity and reproducibility of FFQ used in the current study have been verified, which supports the reliability of the dietary data used in this investigation.[45–48] Third, information about RAAS blockade was not attainable. Considering that RAAS plays important roles in maintaining sodium homeostasis and that RAAS blockade is one of the known factors affecting renal function, data about the type of hypertension medication used would have been informative. Further investigations including these variables are recommended.

In conclusion, this study investigated the association of dietary sodium intake with the risk of CKD development in a community-based prospective cohort with normal renal function. Both high and low sodium intake were associated with an increased risk of CKD, and this relationship was only observed in subjects with hypertension. Lowering sodium intake to preserve renal function may be effective only in patients with hypertension. Nonetheless, caution should be exercised not to overrestrict sodium intake in these patients. Additional controlled trials are needed to further clarify the effect of dietary sodium intake on renal outcome.

MATERIALS AND METHODS

Study population

This study used data from the KoGES, a prospective community-based cohort study. Detailed profile and methods concerning the development of KoGES have been described previously.[42] In brief, the study cohort consisted of 10,030 subjects 40 to 69 years of age who are residents of Ansan (urban area) or Ansung (rural area), which are cities near the South Korean capital of Seoul. The subjects underwent health examinations and various surveys at baseline. Serial health examinations and surveys were performed biennially from 2001 to 2014. For this study, subjects whose dietary information was available at baseline were initially screened. After excluding those with missing data and underlying kidney disease at baseline, a total of 7977 subjects were included in the final analysis. All analyses were performed separately according to the presence of hypertension due to the possibility that dietary sodium would have a different effect on outcome based on the presence of underlying hypertension. A total of 3106 subjects with hypertension and 4871 without hypertension were finally analyzed in the current investigation (Figure 4).

All participants were voluntarily enrolled in the study, and informed consent was obtained for all participants. This study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University Health System Clinical Trial Center (4–2016–0746).

Data collection

All participants underwent a comprehensive health examination and completed questionnaires on health and lifestyle at the time of study

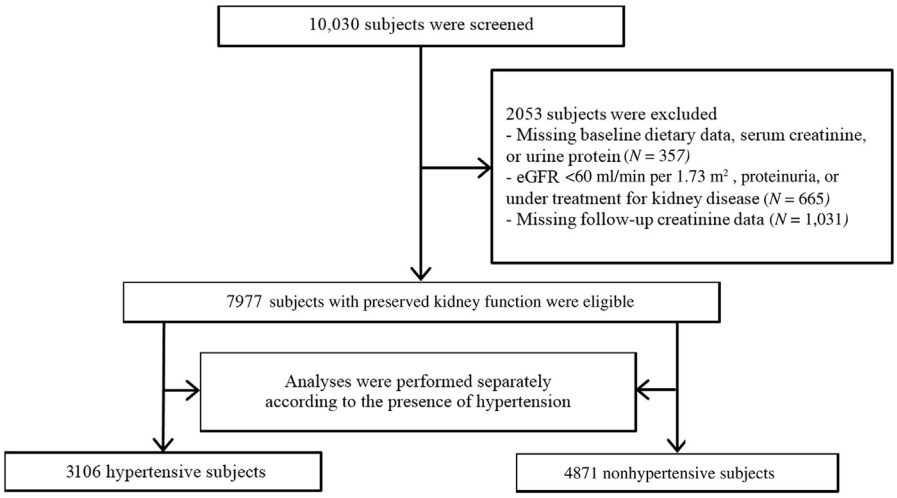

Figure 4 | Flow diagram of study cohort. eGFR, estimated glomerular filtration rate.

entry. Demographic and socioeconomic data including age, sex, level of education, income, marital status, smoking status, alcohol intake, exercise, and medical history were also collected. Anthropometric parameters such as height, body weight, as well as waist and hip circumferences were measured by skilled study workers following standard methods while subjects were wearing light-weight clothing. Body mass index and waist-to-hip ratio were calculated as kg/m^2, and waist circumference was divided by hip circumference. Education status was divided into 3 groups: low, lower than middle school; middle, middle school; and high, higher than middle school. Income status was also divided into 3 groups: low, <$850 per month; middle, >$850 to <$1700 per month; and high, >$1700 per month. Physical activities were expressed as metabolic equivalent of task. Subjects who had a history of hypertension, with a blood pressure of >140/90 mm Hg or were taking antihypertensive medications, were considered hypertensive. Those who had a medical history of diabetes, blood glucose levels of ≥126 mg/dl in 8-hour fasting status, post-load glucose levels of ≥200 mg/dl after a 75-g oral glucose tolerance test, hemoglobin A1c (HbA1c) ≥6.5%, or were receiving oral medication and/or insulin treatment for hyperglycemia were considered to have diabetes. Subjects with a medical history of dyslipidemia or taking medication for lipid control were considered as having dyslipidemia. Cardiovascular disease was defined as the composite of myocardial infarction, congestive heart failure, coronary artery disease, peripheral artery disease, and/or cerebrovascular accident.

The following biochemical data were determined by using fasting blood samples: concentrations of sodium, blood urea nitrogen, creatinine, hemoglobin, glucose, HbA1c, albumin, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and C-reactive protein. Low-density lipoprotein cholesterol was calculated by using the Friedewald formula.[49] Urine samples were collected in the morning after first voiding. Fresh urine samples were analyzed by using URISCAN Pro II (YD Diagnostics Corp., Seoul, Korea). Urine test strip results were based on a color scale that quantified proteinuria as absent, trace, 1+, 2+, or 3+. This scale approximately correlates with urine protein levels of <10, 10 to 20, >30, >100, and >500 mg/dl, respectively.[50] The presence of proteinuria was defined as a urinalysis result higher than trace levels. The eGFR was calculated by using CKD-EPI (epidemiology collaboration equation).[51]

Dietary sodium measurements

Single-day dietary data for sodium (g), total calorie (kcal), protein (g), fat (g), and carbohydrate (g) intake were estimated by semi-quantitative 24-hour dietary recall FFQ that was collected by trained interviewers.[52] The questionnaire consists of a food list, 9 frequency-based intake items, and 3 items of intake amount. Each participant was asked to select the frequency, ranging from "never/seldom" to "3 times per day" (food/dish) or "≥5 times per day" (beverages), as well as the amount, ranging from "small," "medium," to "large," of food they consumed on average over the past year. Data were entered into the cohort epidemiology information system, analyzed by a nutrient database for each connected item, and systemically designed to calculate nutrient and food intake for each participant. The key questions presented to participants were as follows: "Recall the average frequency and amount of food you have consumed over the past year. Please consider the average frequency and amount of the past year, not just recent ones"; and "If your current eating habits differ from what you have been eating for the past year, please refer to your prior eating habits." The FFQ was composed of 103 items selected from the 1998 Korean Health and Nutrition Examination Survey, a nationwide dietary survey representing the entire South Korean population.[43] Validity and reproducibility of the FFQ have been verified previously.[45–48] Total dietary nutrient and calorie components were calculated by using the 2011 nutrient database of the Korean Nutrition Society.

Outcome measures

The primary end point was incident CKD, which was defined as a composite of eGFR of <60 ml/min per 1.73 m^2 and/or the development of proteinuria during the follow-up period. Subjects who were lost during follow-up were omitted in the final analysis.

Statistical analysis

Statistical analysis was performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC) and IBM SPSS software for Windows version 23.0 (IBM Corporation, Armonk, NY). Continuous variables are expressed as median (interquartile range), and categorical variables as number (percentage). Normality of distribution was ascertained by the Kolmogorov-Smirnov test. As mentioned previously, patients were first divided into 2 groups according to the presence of hypertension and were further stratified into quartiles based on their dietary sodium intake. Differences among these 4 groups were determined by analysis of variance or Kruskal-Wallis test for continuous variables, and the χ^2 test for categorical variables. Trend analyses for total calorie intake, potassium intake, and laboratory parameters were conducted by the Jonckheere-Terpstra test. Cumulative renal survival rates were estimated by Kaplan-Meier analysis and a log-rank test. Survival time was defined as the interval between the time of baseline and the last follow-up or outcome. Cox proportional hazards regression analyses were performed to determine the independent predictive value of dietary sodium intake on development of incident CKD. Variables that showed statistical significance in univariate regression analyses were selected for Models 1 and 2. Model 3 included variables that were known to have clinical implication on CKD development in addition to Model 2. Variables included in the best fit model were selected by backward stepping and forward stepping. In addition, Akaike's information criterion, which penalizes log likelihood by the number of estimated parameters and thereby counters the better fit found by adding in extra variables, was also used.[53,54] Evaluation of the possible nonlinear relationship between age or systolic blood pressure and HR of CKD was performed nonparametrically with restricted cubic splines.[55] Tests for nonlinearity used the likelihood ratio test to compare the model with only linear terms to the model with both linear and cubic spline terms. A multiple Cox proportional hazard regression analysis with spline model was constructed for nonlinear variables. All results are expressed as HR and 95% CI. For all analyses, $P < 0.05$ was considered statistically significant.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

Epidemiologic data used in this study were obtained from the KoGES (4851–302) of the Korea Centers for Disease Control and Prevention, Republic of Korea.

AUTHOR CONTRIBUTIONS

Specific contributions made by each author were as follows. CYY and JTP made conception and design of the study; CYY, JN, JL, JTP, SHH,

THY, and SWK analyzed and interpreted data; CYY and JTP drafted manuscript and SHH, THY, and SWK further revised it critically for important intellectual content; CYY, JTP, YKK, CS, ML, MUC, HK, SP, HRY, SYJ, JHJ, SHH, THY, and SWK contributed to discussion; CYY, JTP, and SWK reviewed/edited the manuscript. All authors gave their final approval of the version submitted for publication and agreed to be accountable for all aspects of the work, ensuring that questions related to accuracy or integrity regarding any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Table S1. Baseline characteristics of subjects with hypertension.
Table S2. Baseline characteristics of subjects without hypertension.
Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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Mild Chronic Hyponatremia in the Ambulatory Setting: Significance and Management

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Abstract

Mild chronic hyponatremia, as defined by a persistent (>72 hours) plasma sodium concentration between 125 and 135 mEq/L without apparent symptoms, is common in ambulatory patients and generally perceived as being inconsequential. The association between increased mortality and hyponatremia in hospitalized patients in various settings and etiologies is widely recognized. This review analyzes the significance of mild chronic hyponatremia in ambulatory subjects and its effects on mortality and morbidity. It addresses whether this disorder should even be treated and if so, which patients are likely to benefit from treatment. The available approaches to correct hyponatremia in such patients in the context of recently published panel-generated recommendations and guidelines are described.

Clin J Am Soc Nephrol 10: 2268–2278, 2015. doi: 10.2215/CJN.00170115

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Introduction

Numerous studies have shown a significant association between hyponatremia and mortality in patients admitted to hospitals (1,2) or intensive care units (3,4). This association is consistent and well recognized across a number of etiologies and comorbidities, including heart failure (5), cirrhosis (6), neoplasms (7), and CKD (8). Hyponatremia has been felt to be a marker of severe and advanced disease rather than a direct contributor to excess mortality (9). We reviewed whether the association observed in ill hospitalized patients extends to ambulatory patients with mild chronic hyponatremia who have mild or no symptoms. However, the accompanying brain adaptation to hyponatremia makes them prone to morbidity and treatment-related complications. We present data regarding potential outcomes of mild chronic hyponatremia and its treatment that must be weighed against the benefit afforded by its correction.

Significance of Mild Chronic Hyponatremia

Mild Chronic Hyponatremia and Risk of Mortality

As a part of the baseline evaluation of the Copenhagen Holter Study, Sajadieh *et al.* (10) measured plasma sodium concentration (PNa) in a cohort study aimed at addressing the value of 48-hour Holter recording in risk assessment of 671 subjects without apparent cardiovascular disease. After adjustment for age, sex, smoking, diabetes, LDL cholesterol, and systolic BP, PNa<134 and <137 mEq/L were associated with hazard ratios (HRs) for the composite end point of all-cause mortality or first myocardial infarction of 3.56 (95% confidence interval [95% CI], 1.53 to 8.28; $P<0.05$) and 2.21 (95% CI, 1.29 to 3.80; $P<0.05$), respectively. This association was not driven by myocardial infarction. After excluding diuretic users, even PNa in the range of 135–137 mEq/L was found to be an independent predictor of the composite end point, with an HR of 2.39 (95% CI, 1.10 to 5.18; $P=0.03$).

Hoorn *et al.* (11) measured baseline PNa in 5208 subjects in the Rotterdam Study, a prospective cohort designed to assess risk factors for various ailments in the elderly population. With a prevalence of 7.7%, hyponatremia was an independent predictor of mortality, even after adjusting for demographics and comorbidities, with an HR of 1.21 (95% CI, 1.03 to 1.43; $P=0.02$).

Gankam-Kengne *et al.* (12) analyzed the significance of baseline PNa in the Dallas Heart Study aimed at identifying biologic, ethnic, and socioeconomic determinants of differences in cardiovascular health among 3551 subjects. The prevalence of hyponatremia was 6.3%. After adjustments for demographics, major comorbidities, and other factors, hyponatremia remained an independent risk factor for mortality, with an HR of 1.75 (95% CI, 1.08 to 2.81; $P=0.02$).

In a cross-sectional study, Mohan *et al.* (13) measured PNa in 14,697 adults who participated in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2004. At an estimated prevalence of 1.72%, hyponatremia was associated with an HR of death of 3.61 (95% CI, 2.31 to 5.63; $P<0.001$). Following Cox regression models adjusting for demographics, comorbidities, and other factors, a highly significant association persisted.

Taken together (Table 1), the data strongly support the view that hyponatremia is associated with an increased risk of mortality in outpatients, as it is in those that are hospitalized.

Mild Chronic Hyponatremia and Risk of Morbidity

Neurocognitive Deficits. The adaptive cerebral response to hyponatremia involves the loss of osmolytes, some of which are neurotransmitters (14), making the relationship between hyponatremia and central nervous system impairment biologically plausible. Several excitatory amino acids, such as glutamate, are lost in the adaptation to cell swelling, a process known as regulatory volume decrease (15,16). It is, therefore, not

Table 1. Studies reporting the association of mild chronic hyponatremia and mortality in ambulatory and community settings

Study	Study Design	Cohort Size	Definition of Hyponatremia (mEq/L)	Mean PNa ±SD (mEq/L)	Prevalence of Hyponatremia (%)	Mortality Rate (%) in the Hyponatremic Group	Mortality Risk (Adjusted HR)
Sajadieh *et al.* (10)	Prospective cohort	671	≤134	133[a]	2.1	43[b]	3.56 (95% CI, 1.53 to 8.28)
			≤137	136[a]	9.2	27[b]	2.21 (95% CI, 1.29 to 3.80)
Hoorn *et al.* (11)	Prospective cohort	5208	<136	133.4±2	7.7	51.6	1.21 (95% CI, 1.03 to 1.43)
Gankam-Kengne *et al.* (12)	Prospective cohort	3551	<135	133[a]	6.3	14.4	1.75 (95% CI, 1.08 to 2.81)
Mohan *et al.* (13)	Cross-sectional	14,697	<133 (1999–2002) and <136 (2003–2004)	132.3±2.6	1.72	11	2.43 (95% CI, 2.31 to 5.63)

PNa, plasma sodium concentration; HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Median PNa.
[b]Composite outcome of mortality or first myocardial infarction.

surprising that neurocognitive deficits are evident, even in apparently asymptomatic patients, when such changes are specifically probed for (17) (Table 2).

In a multifaceted landmark study, Renneboog *et al.* (18) performed neurocognitive testing in 16 patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH), with each serving as his/her own control before and after the treatment of hyponatremia. Attention deficits were evaluated by measuring reaction times and error numbers to a series of visual and auditory stimuli presented to the patients, who reacted with a simple motor response. When hyponatremic, the mean latency and error number were statistically higher, even compared with volunteers after moderate alcohol consumption. The threshold PNa at which attention deficits significantly increased was 132 mEq/L.

In a retrospective case-control study, Gosch *et al.* (19) administered the Comprehensive Geriatric Assessment, a standardized tool to screen for functional and cognitive disabilities, to 129 elderly patients with hyponatremia consecutively admitted to a geriatric unit and matched them for age and sex with 129 normonatremic controls. After multivariate analysis, the patients with mild chronic hyponatremia had significantly worse outcomes in the cognitive and functional tests of the Comprehensive Geriatric Assessment compared with controls.

Gunathilake *et al.* (20) evaluated cognitive function in asymptomatic community-dwelling individuals from the Hunter Community Study, a population-based prospective cohort study aimed to assess factors important in elderly health. Cognitive function was higher in individuals with a PNa of 135 mEq/L compared with those with a PNa of 130 mEq/L (95% CI, 1.56 to 7.79; $P=0.01$).

Gait Disturbances. Another component of the study by Renneboog *et al.* (18) evaluated gait by measuring the total traveled way (TTW) after a 10-second tandem walk with eyes opened over a pressure-sensitive calibrated platform. TTW was significantly longer during hyponatremia compared with TTW when PNa was restored to normal (Figure 1). The TTW in the hyponatremic group was even longer than that of volunteers after moderate alcohol intake.

Falls. To assess the significance of gait disturbances, Renneboog *et al.* (18) also studied the prevalence of falls in 122 consecutive patients with hyponatremia and 244 matched controls who presented to an emergency department during a 3-year period. Hyponatremia was associated with a higher prevalence of falls (21.3%) compared with normonatremic controls (5.3%), with an unadjusted odds ratio (OR) of 9.45 (95% CI, 2.64 to 34.09; $P<0.001$). After adjusting for demographics and covariates, the OR for falls in patients with hyponatremia markedly increased (OR, 67.43; 95% CI, 7.48 to 607.42; $P<0.001$). The threshold PNa at which fall risk significantly increased was 134 mEq/L. This observation has been substantiated by later reports (Table 3).

In another small retrospective study of psychiatric patients, Bun *et al.* (21) investigated the association between mild chronic hyponatremia and fall risk; 91 patients with hyponatremia were matched with 157 normonatremic subjects. Using backward stepwise logistic regression, hyponatremia was associated with an increased fall risk (OR, 4.38; 95% CI, 1.33 to 14.46).

The above-described study by Gunathilake *et al.* (20) found not only cognitive deficits but also, after adjusting for

Table 2. Studies reporting the association of mild chronic hyponatremia and neurocognitive deficits

Study	Type of Study	Cohort Size	Mean PNa ±SD (mEq/L)	Neurocognitive Assessment Tool	Outcomes of Hyponatremia
Renneboog *et al.* (18)	Crossover	16	128±3	Battery of attention tests[b]	Median latencies increased by 58 ms ($P<0.001$) and no. of errors increased 1.2-fold ($P=0.001$)
Gosch *et al.* (19)	Retrospective case control	258	128±3.2	MMSE and CC	In multivariate analyses, hyponatremia was a significant predictor for abnormal scores on the MMSE ($P=0.04$; OR, 1.96; 95% CI, 1.05 to 3.68) and CC ($P=0.02$; OR, 2.57; 95% CI, 1.19 to 5.55)
Gunathilake *et al.* (20)	Prospective cohort	2550	135 versus 130[a]	ARCS	Scores were, on average, 4.67 units significantly lower ($P=0.01$)

PNa, plasma sodium concentration; MMSE, Mini-Mental State Examination; CC, Clock Completion test; ARCS, Audio Recording Cognitive Screening tool; OR, odds ratio; 95% CI, 95% confidence interval.
[a]Study compared patients with PNa of 135 versus 130 mEq/L. No mean PNa was provided.
[b]Visual Vigilance, Working Memory or Digit Span, Go/No Go, Intermodal Comparison, Divided Attention, and Phasic Alert.

demographics and diuretic use, that a decrease in PNa from 135 to 130 mEq/L was associated with a 32% increase in fall risk.

Bone Fractures. Several studies have found that hyponatremia-associated gait instability, the most likely proximate cause for the high incidence of falls, also increases fracture risk (Table 4).

Gankam Kengne *et al.* (22) analyzed the association between bone fractures and hyponatremia in ambulatory elderly patients. They identified 513 patients with bone fractures and matched them for age and sex with 513 controls. Hyponatremia was present in 13% of subjects in the fracture cohort but only in 3.9% of controls ($P<0.001$), with an adjusted OR for cofounders of 4.16 (95% CI, 2.2 to 47.71).

Sandhu *et al.* (23) studied 364 patients who presented with a large bone fracture to the emergency room over an 18-month period and matched them with 364 controls; 9.1% of patients with fracture were hyponatremic compared with 4.1% in the fracture-free control group ($P<0.01$). By regression analysis, patients with hyponatremia were 2.5 times more likely to experience a fracture ($P=0.001$).

In a secondary analysis of a retrospective study aimed at the relationship between CKD and fractures, Kinsella *et al.* (24) found hyponatremia in 8.7% of patients with fractures but only in 3.2% of a fracture-free cohort ($P<0.001$). This study determined the OR after adjusting not only for age and CKD stage but also, T-score, osteoporosis risk factors, and treatment. After such adjustments, the OR remained significantly elevated at 2.25 (95% CI, 1.24 to 4.09), suggesting that hyponatremia, independent of bone mineral density (BMD), is a risk factor for fractures.

In the Rotterdam Study, hyponatremia was associated with an increased incidence of nonvertebral fractures, which remained significant (HR, 1.34; 95% CI, 1.08 to 1.68; $P=0.09$), even after adjusting for age, sex, body mass index (BMI), and multiple covariates (11).

In a retrospective case-control study, Tolouian *et al.* (25) assessed the prevalence of hyponatremia in 249 elderly patients admitted with hip fracture and compared it with the prevalence in 44 ambulatory controls concomitantly admitted for elective hip or knee replacement surgery. The prevalence of hyponatremia in cases and controls was 16.9% and 4.6%, respectively. After controlling for age, hyponatremia was associated with an increased hip fracture risk (OR, 4.8; 95% CI, 1.06 to 21.67; $P=0.04$).

Most recently, Jamal *et al.* (26) studied the association of hyponatremia with fractures among 5122 elderly community–dwelling men using data from the Osteoporotic Fractures in Men Study. Baseline prevalence of hyponatremia was 1.25%. Hyponatremia conveyed a higher risk of hip fracture (HR, 3.48; 95% CI, 1.76 to 6.87) as well as a higher risk for prevalent (HR, 2.78; 95% CI, 1.46 to 5.30) and incident (HR, 3.36; 95% CI, 1.36 to 8.27) morphometric fractures (*i.e.*, fractures identified by x-ray rather than from symptoms) compared with normonatremic subjects. After adjusting for cofounders, including falls and low BMD, the relationship between hyponatremia and fractures was not reduced.

It is of interest that the above-mentioned Rotterdam Study found an association between hyponatremia and fractures independent of falls. This argues against a primary role for falls, because vertebral fractures, which were also found to be associated with hyponatremia, are usually not caused by trauma.

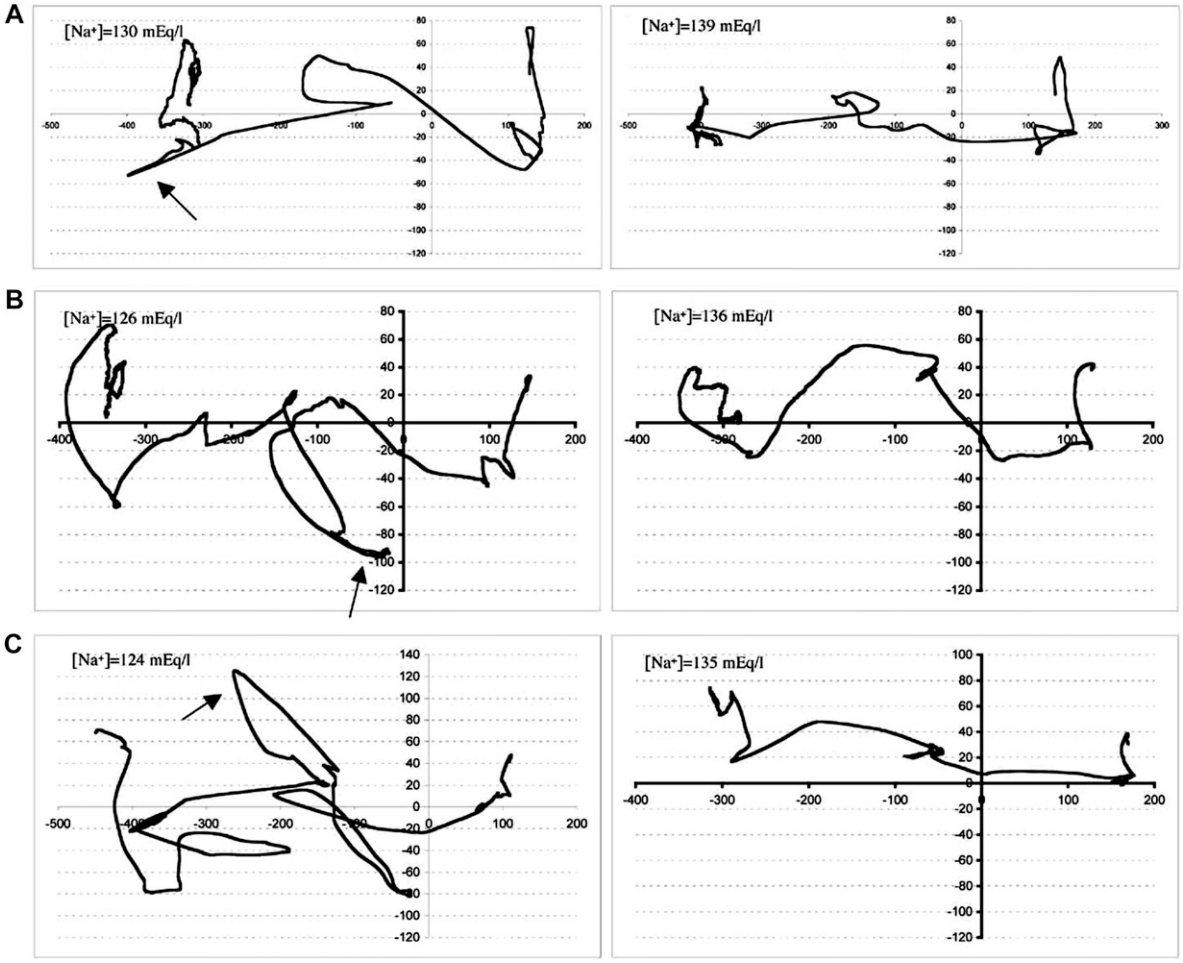

Figure 1. | **Mild chronic hyponatremia is associated with gait disturbances**. The recorded projection of the center of gravity over a pressure-sensitive calibrated platform or total traveled way (TTW) in three patients (A–C) after a 10-second tandem walk from right to left with eyes opened is shown. The left panel shows the TTW during mild chronic hyponatremia, and the right panel shows the TTW after correction of hyponatremia. Irregular paths of the center of pressure were observed in the hyponatremia condition (arrows). Reprinted from reference 18, with permission.

Table 3. Studies reporting the association of mild chronic hyponatremia and falls

Study	Type of Study	Cohort Size	Mean PNa ±SD (mEq/L)	Fall Risk (OR)
Renneboog *et al.* (18)	Cross-sectional	366	126±5	67.43 (95% CI, 7.5 to 607)
Bun *et al.* (21)	Retrospective case control	248	131.82±2.99	4.38 (95% CI, 1.33 to 14.46)
Gunathilake *et al.* (20)	Prospective cohort	2550	135 versus 130[a]	1.32 (95% CI, 1.04 to 1.64)

PNa, plasma sodium concentration; OR, odds ratio; 95% CI, 95% confidence interval.
[a]Study compared patients with PNa of 135 versus 130 mEq/L. No mean PNa was provided.

Osteoporosis. Verbalis *et al.* (27) have undertaken studies to better define the relationship between hyponatremia and bone metabolism using a rat model of SIADH. Hyponatremic rats had a reduction of bone mass of 30% compared with fluid-restricted controls that also received desmopressin but did not develop hyponatremia. There were no significant differences in serum calcium, parathyroid hormone, and urinary calcium excretion between groups. Microcomputed tomography showed a decrease in bone volume, cortical thickness, and trabecular number in all hyponatremic animals compared with controls. Hyponatremia increased the number of osteoclasts per bone area compared with controls, suggesting that increased bone resorption, rather than decreased bone formation, was the predominant mechanism.

Table 4. Studies reporting the association of mild chronic hyponatremia and bone fractures

Study	Type of Study	Cohort Size	Definition of Hyponatremia (mEq/L)	Mean PNa±SD (mEq/L)	All Fracture Risk (OR)
Gankam Kengne *et al.* (22)	Retrospective case control	1026	<134	131±3	4.16 (95% CI, 2.2 to 47.71)
Sandhu *et al.* (23)	Retrospective case control	728	<135	131±2	2.34 (95% CI, 1.24 to 4.35)
Kinsella *et al.* (24)	Retrospective case control	1408	<135	132.2±1.8	2.25 (95% CI, 1.24 to 4.09)
Hoorn *et al.* (11)	Prospective cohort	5208	<136	133.4±2	1.34[b] (95% CI, 1.08 to 1.68)
Tolouian *et al.* (25)	Retrospective case control	293	<135	a	4.8[c] (95% CI, 1.06 to 21.67)
Jamal *et al.* (26)	Prospective cohort	5122	<135	132.3±1.8	3.48[d] (95% CI, 1.76 to 6.87)

PNa, plasma sodium concentration; OR, odds ratio; 95% CI, 95% confidence interval.
[a]Mean PNa not provided in the publication.
[b]Hazard ratio for nonvertebral fractures.
[c]OR for hip fracture.
[d]Hazard ratio for hip fracture.

In a follow-up study, Barsony *et al.* (28) examined the effects of hyponatremia on osteoclast number and activity. Exposure of murine monocytic and bone marrow monocyte culture cells taken from hyponatremic rats to low extracellular sodium concentration, while maintaining a normal extracellular osmolality by the addition of mannitol, directly stimulated osteoclastogenesis and osteoclast activity. These observations have been complemented by the work by Tamma *et al.* (29), which found that vasopressin receptor V1A and vasopressin receptor V2 (V2R) are present in osteoblasts and osteoclasts of wild-type mice and that vasopressin injected into these animals stimulated bone resorption by increasing osteoclast activity and inhibited bone formation by decreasing osteoblast activity through stimulation of V2R. This latter observation suggests that antidiuretic hormone (ADH) directly contributes to osteoporosis.

A cross-sectional study using the NHANES III database that investigated the association between hyponatremia in the general population ages 55 years and older and risk of osteoporosis provides the clinical significance to the above observations (27). After adjusting for age, sex, BMI, physical activity, 25(OH) vitamin D3 level, and diuretic use, hyponatremia (mean PNa was 133±0.2 mEq/L) was associated with an increased risk of osteoporosis at the femoral neck and total hip, with ORs of 2.87 (95% CI, 1.41 to 5.81; $P=0.003$) and 2.85 (95% CI, 1.03 to 7.86; $P=0.04$), respectively.

More recently, Kruse *et al.* (30) studied the association between hyponatremia and osteoporosis in a cross-sectional analysis of dexa scans from 1575 in- and outpatients and their concurrent PNas. Hyponatremia was associated with a lower BMD and bone mineral content at the total hip and lumbar spine in the unadjusted model but lost its significance when adjusted for sex, age, and BMI. However, using multiple regression analysis, a dose-response relationship was found between decreasing PNa and decreasing hip BMD, bone mineral content, and T-score.

In summary, increasing data have accumulated to support the contention that mild chronic hyponatremia, while apparently asymptomatic, is associated with cognitive deficits, gait disorders, and falls. These combined with an effect of hyponatremia to promote bone loss result in an increased fracture risk (31).

Management of Mild Chronic Hyponatremia

Despite the absence of randomized control trials assessing the efficacy of various treatment approaches to mitigate the above-discussed morbidities or the increased mortality associated with hyponatremia, consensus panels in the United States and Europe have put forth expert recommendations and clinical practice guidelines, respectively, for the treatment of such patients in various settings (32,33). We analyze herein the available approaches to treat mild chronic hyponatremia specifically for the ambulatory patient with SIADH (Figure 2). The primary goals in treating hyponatremia are to limit water intake and promote renal water excretion. The latter can be accomplished by increasing urine solute load, decreasing the medullary osmotic gradient responsible for water reabsorption, or inhibiting ADH actions (34).

Limitation of Water Intake

Because water intake in excess of the patient's ability to excrete it is central to the pathophysiology of hyponatremia, the limitation of water intake presents a cogent option for treatment. As such, it is the most common first step taken by most physicians. Fluid restriction should include all fluids and not just water. However, what degree of fluid restriction is needed, and will this approach consistently work on every such patient? To answer these questions, it is helpful to review the normal water balance, which is depicted in Table 5. Accordingly, the amount of fluid restriction required to achieve negative water balance should be less than the sum of urine and insensible losses. An alternative rule of thumb is to restrict fluid in an amount that is 500 ml less than the 24-hour urine volume (32).

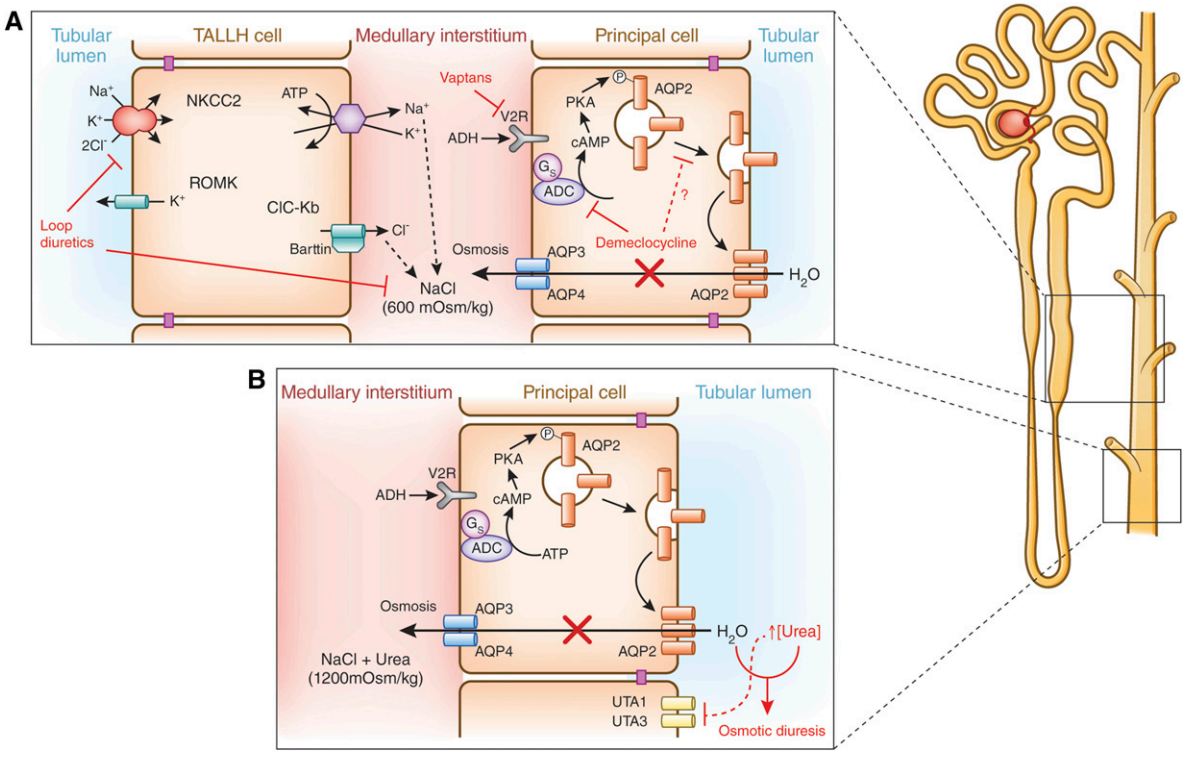

Figure 2. | **Mechanism of action of drugs commonly used to treat hyponatremia**. (A) ADH works by stimulating vasopressin receptors V2 (V2Rs) located in the basolateral membrane of the principal cells in the collecting duct (CD). V2Rs are G_s protein–coupled receptors that, when stimulated, increase cAMP production by adenylcyclase (ADC)-mediated conversion of ATP into cAMP. Elevated levels of cAMP activate protein kinase A (PKA), which in turn, phosphorylates stored aquaporin 2 (AQP2)-containing vesicles and targets them to the apical membrane of CD cells, increasing water permeability. The transport of NaCl into the medulla through the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2), located in the apical membrane of cells in the thick ascending limb of the loop of Henle, is essential for the generation of at least one half of the maximal medullary concentration gradient (600 mOsm/kg), which constitutes a main driving force for water reabsorption along the CD. Loop diuretics work in hyponatremia by inhibiting NKCC2 activity and therefore, interfering with the generation of a hypertonic medulla. Vaptans bind V2R, interfering with ADH action on its receptor. Demeclocycline inhibits ADC enzyme and, perhaps, also has some post-ADC actions. (B) The connecting tubule and cortical and outer medullary CD are impermeable to urea. The inner medullary CD (IMCD) is permeable to urea under the influence of ADH by activation of UTA1 and UTA3. Urea works as an osmotic diuretic in the IMCD, and, probably, along the connecting tubule and CD. In the IMCD, high luminal urea will tend to downregulate urea transporters. In addition, if luminal flow rate is high, there will be less time for urea transport. ADH, antidiuretic hormone; ClC-Kb, basolateral chloride channel; ROMK, renal outer medullary potassium channel; TALLH, thick ascending limb of the loop of Henle, UTA, urea transporters.

A more predictable way to estimate the amount of fluid restriction that is required to achieve changes in PNa is provided by the electrolyte-free water clearance (CeH_20) formula, which represents the amount of free water excreted by the kidneys over a 24-hour period:

$$CeH_20 = V \times \left(1 - \frac{UNa + UK}{PNa}\right)$$

where CeH_20 is the electrolyte-free water clearance, V is the urine volume in 24 hours, UNa is the urine sodium concentration, and UK is the urine potassium concentration.

If information about V is unavailable, ongoing CeH_20 and thereby, its effect on PNa can be assessed from a spot urine by calculating the urine to plasma electrolyte ratio [(UNa+UK)/PNa)]. A (UNa+UK)/PNa>1 indicates a negative CeH_20 (*i.e.*, net free water retention) and predicts a decrease in PNa. Conversely, a (UNa+UK)/PNa<1 reflects a positive CeH_20 (*i.e.*, net free water excretion) and predicts an increase in PNa. The recommended degree of fluid restriction that the ratio predicts is summarized in Table 6 (35).

Patients with SIADH often have (UNa+UK)/PNa>1 and therefore, a negative CeH_20. In such cases, tolerable fluid restriction is not likely to result in improvement of PNa, and additional therapies are usually needed. Other predictors of the likely failure of fluid restriction are urine osmolality >500 mOsm/kg, 24-hour urine volume <1500 ml, and increase of PNa of <2 mEq/L in the first 24–48 hours of fluid restriction <1000 ml/d (32).

Only one randomized study performed in children with acute meningitis addressed the effectiveness of fluid restriction. Fluid restriction was effective at increasing PNa in patients with hyponatremia but did not have any advantage in improving outcomes (36). Furthermore, in data obtained in a recent registry of >3000 subjects with hyponatremia, the increase in PNa observed with fluid restriction in the first 24 hours was not significantly different from that observed in untreated patients (37). PNa usually increases slowly and only by 1–2 mEq/L with fluid restriction alone. Fluid restriction is generally poorly tolerated because of an associated increase in thirst. When fluid restriction fails or is expected to fail, other measures require consideration.

Promoting Renal Water Excretion

Increasing Urine Solute Load.

Enteral Sodium Chloride. Urine solute excretion is a determinant of free water excretion (38). NaCl works in hyponatremia partly by increasing urine solute load, causing an electrolyte diuresis. However, NaCl is used in conjunction with loop diuretics for treating hyponatremia, where its primary role is the restoration of urinary sodium losses and prevention of negative sodium balance (39,40). No trials exist evaluating therapy with NaCl alone, and the very few reported cases using it are combined with loop diuretics. NaCl is available as 1-g (17 mEq sodium and 17 mEq chloride) tablets. Usual doses for NaCl tablets are 6–9 g daily in divided doses (*e.g.*, 2–3 g two or three times per day).

Urea. Urea recycling and its reabsorption in the inner medullary collecting duct (IMCD) by UTA1 and UTA3 transporters play an important role in the fine tuning of renal water reabsorption (41,42). However, urea is an ineffective solute; when its rate of excretion increases (*e.g.*, urea tablets, high-protein diet, post-ATN diuresis, or postobstructive diuresis), urea cannot be absorbed rapidly enough to equilibrate between the tubular lumen and the intracellular space of collecting duct (CD) cells. Under such circumstances, urea becomes an effective solute that obligates water excretion (43). Urea works in hyponatremia by inducing osmotic diuresis and decreasing free water reabsorption in the IMCD (44) and, probably, along the connecting tubule and CD (45). In an animal model, urea improved hyponatremia in SIADH by also decreasing the compensatory natriuresis that contributes to hyponatremia in this syndrome (46). The only clinical evidence for the efficacy of urea in the treatment of hyponatremia comes from case series (47–54). Decaux *et al.* (49) reported seven patients with the diagnosis of chronic SIADH who could not tolerate strict fluid restriction and were treated with oral urea 30 or 60 g/d. Despite normal water intake, urea corrected the hyponatremia in all seven patients (mean PNas pretreatment and during treatment were 115.6±6 and 136±3.5 mEq/L, respectively), with those with higher fluid intake requiring higher doses of urea (60 g/d). Although PNa rose significantly with urea treatment, the concentrations fluctuated widely, and this variation was related to fluctuations in daily water intake. No major side effects were noted after up to 270 days of treatment. Soupart *et al.* (53) also reported the use of urea in a case series of 13 patients with chronic hyponatremia from SIADH. PNa increased from a mean of 125±3 to 135±3 mEq/L at 1 year with the use of vaptans. The vaptans were then discontinued, allowing for recurrence of hyponatremia. Urea was then initiated for an additional 1 year, at the end of which mean PNa was again 135±2 mEq/L. Urea was well tolerated, and no major adverse events were reported. Current European guidelines favor its use as a second-line therapy (after fluid restriction) over the use of vaptans for the treatment of SIADH (33). However, there is no United States pharmacopeia formulation for urea, and it is not approved for this use by the Food and Drug Administration (FDA). Recommended doses are 30–60 g daily in divided doses (49). Urea has many advantages: it acts immediately and has minimal toxic effects, even at plasma concentrations of 193–301 mg/dl. If urine osmolality is high and renal function is well preserved, furosemide is preferred over urea, because it will take a high dose of urea to produce enough osmotic diuresis to be effective (40,55). Urea has been found to be especially effective in the treatment of the nephrogenic syndrome of inappropriate antidiuresis, a genetic disorder caused by activating mutations in the V2R, where vaptans are ineffective (56). BUN and urine osmolality are expected to increase with urea. Urea has a bitter taste, which limits its use, but combining it with sweet-tasting substances, such as orange juice, can alleviate this problem (33,44).

Table 5. Normal water balance

Source	ml
Water input	
Ingested water	1500
Food	800
Metabolic[a]	300
Total	2600
Water output	
Urine	1500
Sweat	100
Stool	200
Insensible losses[b] (TEWL[c] and respiratory)	800
Total	2600

TEWL, transepidermal water loss.
[a]Water generated in the body by the complete oxidation of carbohydrates, fats, and proteins.
[b]Water lost from the body that can be neither perceived nor measured directly.
[c]TEWL is the normal, constitutive loss of water vapor from the skin in the absence of sweat gland activity.

Table 6. Recommended degrees of fluid restriction on the basis of the urine to plasma electrolyte ratio

(UNa+UK)/PNa	Insensible Water Losses (ml)	Water Loss beyond Insensible Losses (ml)	Recommended Fluid Restriction (ml)
>1	800	0–800[a]	0
0.5–1	800	300–800	≤500
<0.5	800	300–800	≤1000

These estimates assume a urine volume of 1 L and a fluid intake closer to the maximal amount allowed by fluid restriction. UNa, urine sodium concentration; UK, urine potassium concentration; PNa, plasma sodium concentration. Modified from reference 35, with permission.
[a]Patients actually could have a negative net water loss (*i.e.*, free water retention) if the urine to plasma ratio is significantly high.

Decreasing Medullary Osmotic Gradient.

Loop Diuretics. The main driver for water reabsorption in the CD is the osmotic gradient generated by the renal medulla, which has tonicity of 1200 mOsm/kg at the level of the papilla. In the inner medulla, NaCl contributes to about 50% of this medullary hypertonicity, with urea contributing to the other 50%. The first step in NaCl transport to the medulla is through the $Na\text{-}K^{+}\text{-}2Cl^{-}$ cotransporter located in the apical membrane of the thick ascending limb of the loop of Henle cells. Loop diuretics inhibit this transporter, reducing NaCl delivered to the medulla and thereby, decreasing the medullary osmotic gradient necessary for water reabsorption in the CD and therefore, increasing free water excretion (57,58). The only clinical evidence for the efficacy of loop diuretics in the treatment of hyponatremia comes from case series, and all in combination with NaCl tablets (39,40,55,59). Of note, most of the patients in these case reports and case series improved their PNa with the combination of loop diuretics and NaCl tablets, despite a relatively normal fluid intake. Although infrequent, there have also been reports of hyponatremia in association with the use of loop diuretics (60,61). The dose of furosemide is 20–40 mg PO one time per day. Loop diuretics act immediately. They are not approved by the FDA to treat hyponatremia.

Inhibiting ADH Actions in the Kidney. Some causes of SIADH (*e.g.*, neoplasms and idiopathic) are not readily reversible. In such cases, consideration should be given to agents that antagonize the renal action of ADH: demeclocycline or vasopressin receptors antagonists.

Demeclocycline. Demeclocycline, a tetracycline derivative, decreases the activity of adenylcyclase and consequently, cAMP synthesis (62,63) and aquaporin 2 abundance in the IMCD (63), resulting in a reversible form of nephrogenic diabetes insipidus. Case series reported modest effects of demeclocycline on improvement of PNa in patients with hyponatremia (64). However, the only clinical trial in existence is a double-blind placebo crossover study with nine psychiatric patients with episodic or chronic hyponatremia caused by primary polydipsia (65). The investigators found no significant difference in the number of episodes of hyponatremia during the period of drug administration versus the placebo period. Nonetheless, demeclocycline is used in refractory cases of hyponatremia. Appropriate dosing of demeclocycline is 600–1200 mg/d in divided doses (62). The onset of action is usually 3 to 4 days (66). Demeclocycline is not approved by the FDA to treat hyponatremia. The use of demeclocycline has been associated with serious adverse reactions, such as skin photosensitivity, risk of superinfection, and nephrotoxicity, especially in patients with cirrhosis (67). Demeclocycline nephrotoxicity seems to be dose dependent, requiring slow dose titration and monitoring of kidney function. Given concerns for serious side effects, the European clinical practice guidelines on the diagnosis and treatment of hyponatremia recommend against its use (33).

Vasopressin Receptor Antagonists (Vaptans). Vaptans directly target the mechanism of hyponatremia in high ADH states by competing with ADH for binding at the V2R in the CD. Tolvaptan is the only oral vaptan approved by the FDA for use in the ambulatory treatment of euvolemic or hypervolemic hyponatremia. The ability of vaptans to increase PNa is amply documented. In fact, vaptans are the only interventions for the treatment of hyponatremia for which there are randomized control trials (*i.e.*, SALT1 and SALT2) (68) complemented by two well conceived meta-analyses (69,70). However, there is a risk of publication bias, because most trials on vaptans, with the exception of the SALT Trials, were done in relatively small numbers of patients, and almost all were sponsored by industry. In addition, there is almost a complete lack of head-to-head trials comparing vaptans with other used therapies. To avoid overcorrection, vaptans must be initiated and reinitiated as inpatient with frequent PNa monitoring. Tolvaptan is started at a dose of 15 mg daily. It may be increased to 30 mg after 24 hours and then, 60 mg after another 24 hours. To mitigate the rate of PNa increase, patients should not be fluid restricted for the first 24 hours. Long-term administration for up to 4 years suggests maintenance of effectiveness (71).

Several limitations must be considered in the use of vaptans. As is also the case with urea and demeclocycline, vaptans are contraindicated in hypovolemic hyponatremia and are not indicated in patients with severe neurologic symptoms, such as seizures, because they have not been tested in such subjects and the onset of changes in PNa is not rapid enough (at least 4–8 hours) to promptly address the symptoms. Vaptans are metabolized by CYP3A4, and therefore, caution should be exercised when coadministered with CYP3A4 inhibitors (*e.g.*, ketoconazole) or inducers (*e.g.*, rifampin), which increase or decrease drug levels, respectively. More recently, concerns regarding liver toxicity have emerged. The TEMPO 3:4 Study designed to determine the efficacy and safety of tolvaptan in the treatment of autosomal dominant polycystic kidney disease (72) reported an increase in liver function tests in the tolvaptan group compared with the placebo group. It is worth mentioning that the dose of tolvaptan used in this study was four times the dose used in the hyponatremia trials, in which no such toxicity was observed. The FDA recommends against using tolvaptan in patients with liver disease or for a period >30 days.

The development of osmotic demyelination syndrome (ODS) is always a concern when hyponatremia is corrected. Although PNa reached the hypernatremic range in some patients involved in the mentioned trials, ODS was not reported in any of them. Since then, in total, 12 patients with ODS in association with tolvaptan have been reported. Only two of those cases have been published (S.A.A. Harb and C. Alraies, unpublished data) (73). However, some other factors could have contributed to PNa overcorrection in the published cases. In the first case, tolvaptan was continued for 4 days, despite an initial increase of PNa from 126 to 142 mEq/L, with further overcorrection to 181 mEq/L by day 4 when tolvaptan was finally stopped. In the second case, the use of tolvaptan was in close temporal relationship with hypertonic saline use. The other 10 unpublished cases have been reported to the FDA (74). These adverse events generated a letter of warning from the producing company (75). A failure to respond to vaptans may occur in some settings (76). These include the presence of very high circulating ADH levels, a vasopressin-independent diluting defect (low distal delivery as a consequence of decreased GFR and enhanced proximal tubular reabsorption as in advanced heart failure or cirrhosis), excessive water intake, and the nephrogenic syndrome of inappropriate antidiuresis (56).

Notwithstanding the well established effects to increase PNa, there are no data to ascertain whether vaptans affect the above-described mortality or alter the risk for various morbidities associated with hyponatremia. Likewise, there is uncertainty as to whether vaptans decrease health resources use by affecting hospitalization rates and length of stay. There was a statistically insignificant trend in this direction in an analysis of the EVEREST Trial (77) and a significant effect in the SIADH subgroup in a *post hoc* analysis of the SALT Trials (78). However, for the average patient, the cost of vaptans remains an impediment for their use (79). The lack of mortality and morbidity benefit coupled with concerns about efficacy and safety led the European practice guidelines committee to not recommend the use of vaptans in euvolemic hyponatremia and even recommend against its use in hypervolemic hyponatremia (33). This is in stark contrast to the recommendations of an expert panel that views the use of vaptans as a reasonable option in both settings (32). It should be noted that the latter panel was supported by funding from Otsuka America Pharmaceuticals Inc., the manufacturer of tolvaptan, and that a substantial proportion of the panel members also had funding from Otsuka America Pharmaceuticals Inc.

Conclusions

Mild chronic hyponatremia is not benign as previously thought and can directly contribute to increased morbidity and possibly, mortality (31,80). Although some of the above pathology is clearly related to hyponatremia, whether treating the disorder will reverse this sequence of events is not yet known. We are of the opinion that patients with mild chronic hyponatremia associated with unstable gait, recurrent unexplained falls, a high fracture risk, or severe osteoporosis might benefit from treatment. The benefits versus risks probably shift in favor of the long-term ambulatory use of tolvaptan when fluid restriction and all other therapies have failed. We recommend that future studies address the following issues: (*1*) the efficacy, safety, and tolerability of urea in the treatment of hyponatremia; (2) the efficacy and safety of vaptans compared with other therapies; and (*3*) the effects of vaptans and other therapies on meaningful patient outcomes, such as falls and fractures.

Disclosures

H.R.B. receives no financial support. T.B. was on the speaker's bureau of Otsuka America Pharmaceuticals Inc. He was also the principal investigator of the SALTWATER Trial, a trial that was sponsored by Otsuka America Pharmaceuticals Inc. T.B. currently does not have any relationship with Otsuka America Pharmaceuticals Inc. He receives no payments, does not own any stock, and has no other conflicts of interest.

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Published online ahead of print. Publication date available at www.cjasn.org.

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Clinical Kidney Journal, 2018, vol. 11, no. 4, 581–585

doi: 10.1093/ckj/sfy016
Advance Access Publication Date: 16 March 2018
CKJ Review

CKJ REVIEW

Hyponatremia in kidney transplant patients: its pathophysiologic mechanisms

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ABSTRACT

Kidney transplant patients (KTPs), and particularly those with advanced chronic kidney rejection, may be affected by opportunistic infections, metabolic alterations and vascular and oncologic diseases that promote clinical conditions that require a variety of treatments, the combinations of which may predispose them to hyponatremia. Salt and water imbalance can induce abnormalities in volemia and/or serum sodium depending on the nature of this alteration (increase or decrease), its absolute magnitude (mild or severe) and its relative magnitude (body sodium:water ratio). Hyponatremia appears when the body sodium:water ratio is reduced due to an increase in body water or a reduction in body sodium. Additionally, hyponatremia is classified as normotonic, hypertonic and hypotonic and while hypotonic hyponatremia is classified in hyponatremia with normal, high or low extracellular fluid. The main causes of hyponatremia in KTPs are hypotonic hyponatremia secondary to water and salt contraction with oral hydration (gastroenteritis, sepsis), free water retention (severe renal failure, syndrome of inappropriate antidiuretic hormone release, hypothyroidism), chronic hypokalemia (rapamycin, malnutrition), sodium loss (tubular dysfunction secondary to nephrocalcinosis, acute tubular necrosis, tubulitis/rejection, interstitial nephritis, adrenal insufficiency, aldosterone resistance, pancreatic drainage, kidney–pancreas transplant) and hyponatremia induced by medication (opioids, cyclophosphamide, psychoactive, potent diuretics and calcineurinic inhibitors). In conclusion, KTPs are predisposed to develop hyponatremia since they are exposed to immunologic, infectious, pharmacologic and oncologic disorders, the combinations of which alter their salt and water homeostatic capacity.

Keywords: hyponatremia, immunosuppressant, kidney transplant, low serum sodium, pathophysiology

INTRODUCTION

Renal transplantation is currently the most effective treatment for patients with end-stage renal disease [1]. However, this group of patients, and particularly those with advanced chronic kidney rejection, are sometimes affected by opportunistic infections, metabolic alterations and vascular and oncologic diseases that require treatments, the combination of which predisposes them to hyponatremia [2]. Hyponatremia is considered an important risk factor for high morbidity and mortality because it can decrease brain function, compromise cardiac contractility, increase insulin resistance and induce neuromuscular dysfunction. Han *et al.* [3] documented that hyponatremia is related in kidney transplant patients (KTPs) to overall mortality and graft loss, although it had

Received: 1.11.2017. *Editorial decision:* 18.1.2018

Table 1. Mechanisms of hyponatremia in kidney transplant, their prevalence and clinical relevance

Hyponatremia	Prevalence	Clinical relevance	Treatment
Normotonic	–	–	–
Intravenous immunoglobulin	High	Low	Resolves after stopping drug
Hypertonic	–	–	–
Hyperglycemia	High	Low	Glycemic control
Hypotonic with low ECF	–	–	–
Renal sodium loss (rejection, diuretics)	High	High	Sodium replacement and treat cause
Extrarenal sodium loss (diarrhea)	High	High	Sodium replacement and treat cause
Adrenal insufficiency	High	High	Hormone replacement
Immunosuppressant drugs	High	Low	Fludrocortisone
Hypotonic with high ECF	–	–	–
Heart failure	Low	High	Salt and water restriction/diuretics
Cirrhosis	Low	High	Salt and water restriction/diuretics
Nephrotic syndrome	High	High	Salt and water restriction/diuretics/treat cause
Renal insufficiency	High	High	Salt and water restriction/diuretics/dialysis treat cause
Hypotonic with normal ECF	–	–	–
SIADH	High	High	Water restriction/diuretics
Hypothyroidism	Low	Low	Hormone replacement
Glucocorticoid deficiency	Low	High	Hormone replacement
Psychoactive drugs	High	Low	Replace drug

no correlation with acute rejection. Thus serum sodium should be monitored posttransplant in order to prepare physicians for potentially poorer outcomes. Moreover, pediatric kidney transplant recipients are at a significantly higher risk than adults for developing hyponatremic encephalopathy and death associated with serum sodium levels $\leq$120 mmol/L, thus meticulous postoperative fluid management is exceptionally important to minimize the risk of neurologic complications in this population [4]. Salt and water imbalance can induce abnormalities in volemia and/or serum sodium depending on the nature of this alteration, its absolute magnitude and how they alter the relative body sodium:water ratio [5]. It is known that significant salt and water depletion may generate real hypovolemia, and if this depletion involves a loss of salt in excess of water it may generate hyponatremia [3]. Also, salt and water retention induces an increase in extracellular fluid (ECF) that, depending on its pathophysiologic mechanism, may occur with hypervolemia and edema (e.g. hyponatremia in immediate posttransplant anuric patient) or effective arterial hypovolemia and edema (hyponatremia in a KTP suffering from cirrhosis secondary to hepatitis C virus or hyponatremia secondary to posttransplant nephrotic syndrome most frequently induced by focal and segmental glomerular sclerosis or membranoproliferative glomerulonephritis) [5, 6]. The sodium:water ratio can also be modified by body potassium content since its intracellular depletion induces low serum sodium levels by at least two mechanisms [5]: a shift of sodium to the intracellular compartment and by inappropriate antidiuretic hormone release.

This concept is summarized by the Edelman equation [5]: serum sodium = body (exchangeable) sodium + body (exchangeable) potassium/total body water. For instance, hyponatremia secondary to hypokalemia in KTPs on rapamycin, loop diuretics (e.g. furosemide) or suffering from renal tubular acidosis (primary or secondary to graft rejection) [7–12]. Additionally, two infrequent causes of hyponatremia in KTPs should be mentioned: first, a low serum sodium level due to excessive water intake (>14 L/day), which overcomes the free water excretion capacity of the kidneys and characteristically occurs with suppressed antidiuretic hormone and low osmolar urine [1, 5]; second, a reset osmostat hyponatremia, which can be observed in malnourished chronically ill KTPs [5]. Based on the above-mentioned pathophysiological mechanisms, hyponatremia is currently classified depending on the patient's plasma tonicity level as hypertonic, normotonic or hypotonic hyponatremia. In addition, hypotonic hyponatremia is classified depending on the patient's ECF status as low, normal or high ECF [5]. It is worth mentioning that hyponatremia in KTPs usually results from a combination of hyponatremia-inducing mechanisms. All the hyponatremia-inducing mechanisms in KTPs that are described here are summarized in Table 1 along with their prevalence and clinical significance [3, 4, 7, 10–12].

HYPONATREMIA

Normotonic hyponatremia

Normotonic hyponatremia is an artifact due to an increase in the solid fraction of plasma, which can be documented in KTPs who received intravenous (IV) immunoglobulin (hypersensitive patients) or in those who have severe hypergammaglobulinemia secondary to hepatitis C [13–19]. It is worth mentioning that it is important to identify pseudohyponatremia because treating this entity as hypotonic hyponatremia may lead to dehydration [16, 17]; a direct ion-sensitive electrode potentiometry-based estimation can avoid this mistake [20].

Hypertonic hyponatremia

Hyperglycemia increases extracellular tonicity and extracts free water out of the intracellular compartment, diluting the extracellular compartment and consequently inducing hyponatremia [3]. Thus this sort of hyponatremia can be observed in a setting of drug-induced diabetes mellitus decompensation (high doses of methylprednisolone, high serum levels of calcineurinic inhibitors or a combination of both drugs), sepsis in kidney transplant diabetic patients (predisposed by immunosuppressant treatment) or pancreas graft rejection in kidney–pancreas transplant patients [20–22]. Additionally, even though hyponatremia induced by IV immunoglobulin has been interpreted as a pseudohyponatremia, other reports have documented that this

therapy can result in true hyponatremia, resulting from sucrose-induced translocation of water from the intracellular compartment to the extracellular compartment, as well as a large volume of hypotonic fluid in patients who have altered urinary free water excretion [14].

Hypotonic hyponatremia

Hypotonic hyponatremia can be induced by an excess of water, impaired free water urine excretion because of reduced fluid delivery (heart failure) to the thick ascending limb of the loop of Henle (TALH), altered TALH segment function (tubular necrosis or inflammation), inappropriate or appropriate antidiuretic hormone release or a combination of these [5]. Thus patients with lung (pneumonia, etc.), cardiac (cardiac failure), kidney (renal insufficiency), hepatic (cirrhosis), endocrine (hypothyroidism, adrenal insufficiency) and encephalic diseases [psychiatric disorders, syndrome of inappropriate antidiuretic hormone release (SIADH), cerebral salt wasting syndrome] can develop hypotonic hyponatremia [5].

Normal ECF hyponatremia. *SIADH*. SIADH is a condition induced by inappropriate free water retention because of inappropriate antidiuretic hormone release or an excessive response of vasopressin receptors in the distal tubules in a setting of normal glomerular filtration rate, thyroid and adrenal function and no hyponatremia-inducing medication [5]. SIADH has been described in this population as secondary to infection (tuberculosis, etc.), mainly in the central nervous system (cerebral nocardiosis, etc.) [23–25]. Other mechanisms of hyponatremia with normal ECF that should be taken into account in this population are hypothyroidism-induced hyponatremia and glucocorticoid deficiency–induced hyponatremia

Hypothyroidism-induced hyponatremia. Hypothyroidism can induce low serum sodium levels by different mechanisms: renal hypoperfusion due to heart failure, inappropriate vasopressin secretion and high sodium loss in urine [26–32]. It worth mentioning that it should rule out in persistently hyponatremic-immunosuppressed individuals the presence of a hypothyroidism secondary to a decrease in hypothalamic thyrotropin-releasing hormone (TRH) induced by a masked wasting syndrome [32, 33].

Glucocorticoid deficiency–induced hyponatremia. Cortisol exerts a negative effect on antidiuretic hormone secretion, thus a cortisol deficit can promote inappropriate antidiuretic hormone release, in turn increasing the risk of developing hyponatremia [5]. The isolated cortisol deficit can be induced by any glucocorticoid axis damage [34].

Low ECF hyponatremia. Hypovolemia may induce low serum sodium levels by stimulating nonosmotic antidiuretic hormone release in a setting of adequate or excessive oral water intake [5]. Sodium losses lead to volume depletion inducing adequate antidiuretic hormone secretion. Thus low serum sodium level is promoted by two mechanisms: sodium loss and water retention. Moreover, sodium loss is worsened when there is reduced renin–angiotensin–aldosterone system (RAAS) activity (e.g. tubular damage or adrenal failure) [5].

Pancreatic sodium loss. Low ECF hyponatremia is common in pancreas–kidney transplant patients and is usually attributed to sodium loss in the pancreatic exocrine secretion drained in the bladder [21]. Genitourinary tract (GT) drainage compared with the alternatives (pancreatic duct ligation or enteric drainage) is less prone to develop pancreatitis or microbial contamination, respectively, and also provides the opportunity to monitor urine pH and amylase levels for detecting pancreas rejection. However, GT drainage may induce cystitis, balanitis and/or hyperchloremic metabolic acidosis and hyponatremia secondary to increased sodium bicarbonate urinary loss [21, 22, 35]. At least two pathophysiologic mechanisms have been postulated for this sort of hyponatremia: total body sodium depletion through urinary volume and altered free water clearance secondary to renal failure. In this setting, hyponatremia usually gets worst if the kidney is simultaneously suffering from tubular damage (necrosis, rejection, etc.) and therefore is unable to maximally conserve sodium [22].

Massive posttransplant polyuria. Polyuria after kidney transplantation is not a rare condition, but massive polyuria is not common [34]. This entity can lead to significant sodium wasting and consequently to hyponatremia, and eventually to cerebral edema and seizure activity [26]. This sodium loss is secondary to tubular dysfunction induced by hypoxic-ischemic graft injury and aldosterone resistance in a context of a rapid normalization of the glomerular filtration rate [26, 36]. In these cases, the high fractional excretion of sodium reported in the graft urine is characteristically associated with ischemic changes on the graft biopsy [26].

Sodium-losing nephropathy. Altered tubular function in the transplanted kidney is common (more so in cadaveric donors than in living donors) and most is ascribed to tubular necrosis or graft rejection; this can improve if the acute process resolves. Other proposed pathophysiologic mechanisms are the presence of RAAS resistance, graft nephrocalcinosis (tubular necrosis or rejection) or a carryover effect of pre-transplantation 'third factor'. Sodium-losing nephropathy is characterized by severe sodium loss (fractional excretion of sodium ~38%) with nonoliguric (neither polyuric) renal failure that responds to large amounts of normal saline and a high sodium diet but not to mineralocorticoid therapy [36].

Fanconi syndrome (FS). FS is another source of urine sodium loss inducing hyponatremia. FS can appear in children or adult transplant patients who have received a cadaveric or living donor kidney. FS can be induced by hyperparathyroidism, tubular disease or rejection [8, 9, 37–41].

Adrenal insufficiency. The hypothalamic–pituitary–adrenal axis (HPAA) can be activated by severe illness and trauma, since HPAA controls the maintenance of homeostasis and general adaptation to stress by increasing corticotropin and cortisol serum concentrations. However, in KTPs on chronic corticoid therapy, adrenal gland function is suppressed due to exogenous steroids and cannot resume steroid synthesis. Thus, relative adrenal insufficiency must be considered in patients who have received prolonged glucocorticoid therapy and have symptoms such as hypotension and/or hyponatremia, even in the context of normal serum cortisol levels, since they can be relatively low [42, 43].

High ECF hyponatremia. This condition is observed in KTPs when they are suffering from severe edematous status, which could be secondary to nephrotic syndrome, and renal, heart or liver failure. In these settings of effective hypovolemia, low

Table 2. Hyponatremia-inducing mechanisms secondary to drugs

Salt wasting	Water retention	Undefined mechanism
a. Tubular toxicity (tacrolimus, cyclosporine) b. Interstitial nephritis (trimethoprim, loop diuretics, thiazide)	a. Severe renal insufficiency (tacrolimus, cyclosporine) b. Cortisol deficiency (rifampicin, ketoconazol) c. SIADH effect (opioids, antidepressants, cyclophosphamide)	a. Amphotericine B, pentamidine

serum sodium is induced because of impaired circulatory delivery to diluting segments combined with adequate antidiuretic hormone release [5]. In hypervolemic states, low serum sodium level is induced by impaired free water excretion due to glomerular filtration rate reduction (<5 mL/min/1.73 m^2) [5]. Renal insufficiency is one of the kidney transplant complications that can be secondary to tissue necrosis, intratubular obstruction (luminal accumulation of necrotic tubular cells) and tubulointerstitial and vascular damage (kidney rejection). In this setting, hypotonic solution overload contributes to the appearance of hyponatremia [21, 44].

Drug-induced hyponatremia. Drug-induced hyponatremia is one of the main causes of hyponatremia in KTPs and therefore this type of hyponatremia is described here separately [5]. Medication can induce hyponatremia by different mechanisms that promote water retention and/or sodium loss (Table 2) [7, 22, 38, 45–49]. High-dose IV cyclophosphamide (30–50 mg/kg), opioids and psychoactive drugs, which are usually used in transplantation, may cause water intoxication [7, 49]. Regarding calcineurinic inhibitors (tacrolimus and cyclosporine), studies have suggested that cyclosporine reduces proximal tubular sodium reabsorption by decreasing sodium–hydrogen exchanger activity, which is responsible for reabsorbing 30–60% of the filtered sodium, while tacrolimus has a more profound effect on distal tubular function, where it alters tubular sodium handling, which is responsible for aldosterone resistance, and can cause salt-losing nephropathy [21, 47, 49–51]. This phenomenon explains why hyponatremia was reported as significantly more common under tacrolimus therapy than cyclosporine treatment in transplant patients, and also the ineffectiveness of fludrocortisone for treating tacrolimus-induced hyponatremia [21, 22].

CONCLUSION

KTPs are predisposed to develop hyponatremia since they are exposed to immunologic, infectious, pharmacologic and oncologic disorders, the combination of which alters their salt and water homeostatic capacity.

CONFLICT OF INTEREST STATEMENT

None declared.

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Hyponatremia and the Brain

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Hyponatremia is defined by low serum sodium concentration and is the most common electrolyte disorder encountered in clinical practice. Serum sodium is the main determinant of plasma osmolality, which, in turn, affects cell volume. In the presence of low extracellular osmolality, cells will swell if the adaptation mechanisms involved in the cell volume maintenance are inadequate. The most dramatic effects of hyponatremia on the brain are seen when serum sodium concentration decreases in a short period, allowing little or no adaptation. The brain is constrained inside a nonextensible envelope; thus, brain swelling carries a significant morbidity because of the compression of brain parenchyma over the rigid skull. Serum sodium concentration is an important determinant of several biological pathways in the nervous system, and recent studies have suggested that hyponatremia carries a significant risk of neurological impairment even in the absence of brain edema. The brain can also be affected by the treatment of hyponatremia, which, if not undertaken cautiously, could lead to osmotic demyelination syndrome, a rare demyelinating brain disorder that occurs after rapid correction of severe hyponatremia. This review summarizes the pathophysiology of brain complications of hyponatremia and its treatment.

Kidney Int Rep (2018) **3,** 24–35; https://doi.org/10.1016/j.ekir.2017.08.015
KEYWORDS: brain edema; hyponatremia; osmolarity; serum sodium

Plasma osmolality refers to the quantity of solute dissolved into 1 kg of plasma.[1,2] The serum is separated from the inside of the cell by the cell membrane. The cell membrane is highly permeable to water but not to some ions (e.g., potassium and sodium), and is called semipermeable. The ability of water to move across the cell membrane is related to the tonicity of the plasma that determines the direction and the magnitude of water movement.[3]

The serum sodium (SNa) concentration is the main extracellular osmolyte, and therefore, the most important determinant of serum osmolality.[4] The permeability of the cell membrane to water is due to the presence of water channels called aquaporins (AQPs) that mediate bidirectional water transport.[5] In the central nervous system (CNS), the blood−brain barrier (BBB) separates the brain parenchyma from the plasmatic space. The BBB is composed of several layers; the outermost layer is astrocyte end-feet, which is responsible for water exchange between the brain parenchyma and the vascular space.[6] Astrocyte end-feet express a high number of AQP 4, but other forms of AQP have been identified in astrocytes and other CNS cell types.[5]

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Received 8 June 2017; revised 23 August 2017; accepted 28 August 2017; published online 1 September 2017

At equilibrium, extracellular osmolality equals intracellular osmolality, and the net movement of water across the cell membrane is null. When the SNa concentration is reduced, hypo-osmolality and hypotonicity will ensue, and the water will flow from the extracellular space into the intracellular compartment. This movement of water into the cell will cause cell swelling, and conversely, in the presence of hypertonicity, cells will shrink because of water movement from inside to outside the cell. In the mammalian CNS, even minimal changes in the intracellular volume and the associated brain swelling or shrinking might lead to dramatic symptoms. Macromolecular crowding refers to the behavior of protein inside the cell with respect to the salt and water content of the cytoplasm.[7] It has been shown that many cellular functions (e.g., enzymatic activity) depend of the ionic strength of the cytoplasm, the cell volume, and the macromolecular crowding.[8] Therefore, the maintenance of a normal cell volume and normal intracellular ionic strength is essential. The ability to respond to brisk changes in extracellular osmolality has been evolutionarily conserved across species throughout the evolution process.

The present review details the mechanisms of brain adaptation to hyponatremia, the consequences of hyponatremia on the brain, and discusses the treatment of hyponatremia and the risk associated with excessive correction of SNa from a neurological perspective.

MECHANISMS OF BRAIN CELLS ADAPTATION TO HYPO-OSMOTIC CHALLENGE

Cells have developed several mechanisms to counteract the deleterious effect of extracellular hypotonicity on cell volume. These mechanisms are collectively called regulatory volume decrease (RVD) because their aim is to restore the initial volume after swelling induced by hypotonicity.[9] They essentially involve the extrusion of intracellular osmotically active solutes that will induce obligated intracellular loss of water and prevent or reduce cell swelling. RVD has been well studied in isolated brain cells, mostly in astrocytes and neurons.[10–13] Neuronal cell lines exposed to hypotonicity quickly experience an increase in their volume up to 2-fold in the first minutes, and after a slow decrease in the volume, this reaches a plateau at approximately 60% to 80% of volume recovery in the first 15 minutes.[11] The same is true for glial cell lines.[10] However, these observations should be interpreted along with some caveats. First, not all neuronal cells react alike during hypo-osmolality; some differences have been noted across different neuronal cells.[14] Second, most studies done on RVD in brain cells used either cultured or immortalized cell lines that displayed notable differences with *in vivo* cells. Lastly, regional variability and interspecies variability in glial phenotype have been described, which might have an impact on some biological functions.[15–17] Therefore, it is possible that not only do *in vivo* astrocytes not exhibit the exact same behavior as *in vitro* astrocytes when confronted with hypotonic stress, but also that not all astrocytes in the brain exhibit the same pattern of changes during hyponatremia.

Cellular Mechanisms of RVD, Osmotic Sensing, Signal Transduction, and Efflux Pathways

An osmolyte is a noncell membrane permeable substance that can exert a net movement of water across a semipermeable membrane. Osmolytes are categorized as electrolytes and nonelectrolyte or organic osmolytes. The most common electrolyte osmolytes present in the mammalian brain are sodium, potassium, and chloride ions, and the most common organic osmolytes are myoinositol, betaine, glutamine, taurine, and γ-aminobutyric acid.

The occurrence of RVD implies a sensor for extracellular osmolality, a signal transducer that will translate the information on extracellular osmolality to the channels responsible for intracellular osmolyte depletion. The word osmosensor refers to a sensory element that can detect changes in plasma osmolality.[18] In the mammalian brain, the true nature of the osmosensor is still elusive. The transient receptor potential vanilloid 4 (TRPV4) channel is a member of the broader class of the TRPV channel family that has been shown to be essential for tonicity sensing and transduction trough modulation of calcium influx in several cell lines.[19] In cortical astrocytes and muller glia (retinal glial cells), TRPV4 forms a molecular complex with AQP 4, the main water channel present in astrocyte end-feet. The integrity of that molecular complex is necessary for calcium influx, which has been linked to RVD with an hypo-osmotic challenge.[20,21] Other researchers have suggested that calcium influx is not essential for RVD, and also that inhibition of the TRPV channel does not significantly affect RVD in astrocytes.[22] Because of the complexity and the importance of the process, it is likely that osmosensing operates through at least a few redundant pathways that might not be identical for all brain cells.

Upon sensing, the hypo-osmotic signal must be transduced inside the cell, and protein kinases and calcium are believed to be involved in the transduction of the signal of RVD in astrocytes and neurons. For example, inhibition of protein kinase C can significantly reduce the efflux of potassium and taurine in hypo-osmotically challenged glial cells, which suggests that G-coupled protein receptor with protein kinase C activity is a likely transducer for hypo-osmotic stimuli.[23] After signal transduction, the osmolyte must flow inside or outside the cell trough special channels. The responsible channels for intracellular electrolytes depletion are collectively called volume sensitive channels (for review, see Strange *et al.*[24]). They have been identified in nearly all CNS cells.[25–27] Although these channels can be blocked pharmacologically, their precise identities remain elusive. As for organic osmolytes, several organic osmolyte transporters have been identified in the mammalian brain. For example, these include the γ-aminobutyric acid−betaine transporter and the sodium myoinositol transporter.[28] The channels are bidirectional, and the movement of organic osmolytes through them is dependent on the net concentration gradient. Some interconnections between the volume sensitive channel and the organic osmolyte channels have been described.[29]

Brain Adaptation to Hyponatremia

After onset of systemic hypotonicity from hyponatremia, the brain water content will increase to commensurate the extent of the hyponatremia if the brain behaves like a perfect osmometer. However, studies have shown that after either chronic or acute hyponatremia, the brain water content does not increase as predicted. For instance, after 6 hours of hyponatremia, the brain only increases by 40% of what is predicted, and after 4 days of hyponatremia,

there is only a 0.6% of increase in the brain water content.[30] These observations point to the fact that the brain possesses some defense mechanisms that minimize organ swelling upon plasma hypotonicity. Although sometimes presented as distinct, brain adaptation to acute and chronic hyponatremia belongs to the same physiological spectrum, but some of the mechanisms are of early onset, with rapid exhaustion, whereas others occur in a prolonged timeframe. The clinical distinction between acute and chronic hyponatremia is often set between 24 and 48 hours. This distinction is arbitrary, but it is believed that the reasons for such a cutoff reflect the time frame after which complete mechanisms of brain adaptation are in place, thus making correction of hyponatremia potentially harmful for the brain. Figure 1 depicts brain mechanisms of adaptation to hyponatremia.

Early Mechanisms of Brain Adaptation to Hyponatremia

One of the first mechanisms of defense of the brain against hypotonicity is the water flow from brain parenchyma into the cerebrospinal fluid (CSF) and later into systemic circulation.[32,33] Within the first minutes of hyponatremia, it is believed that the increased pressure inside the brain will drive a hydrostatic water movement inside the CSF first and then into the systemic circulation. This will work as a first guard to prevent rapid brain edema. For example, in a new-born rat pup with a soft skull in which brain edema does not cause an increase in hydrostatic pressure, there is no water flow from the brain to the CSF.[34]

Another step of brain cell adaptation to hyponatremia involves movement of electrolytes from inside the cell to the extracellular compartment. Within the first hours of hyponatremia, there is a significant decrease in the intracellular content of sodium, chloride, and potassium.[31,35] The kinetics of brain electrolytes depletion during acute hyponatremia revealed that after 3 hours of hyponatremia, brain depletion in electrolytes reaches a plateau, and the depletion of sodium is believed to be primarily from the CSF, which occurs together with intracellular depletion of chloride faster than the intracellular depletion of potassium.[30] The total brain ion depletion is roughly similar (~18%) within a large range of hyponatremia (72–116 mEq/l), which strongly suggests the brain can lose no more than 18% of its ion content. Because of this

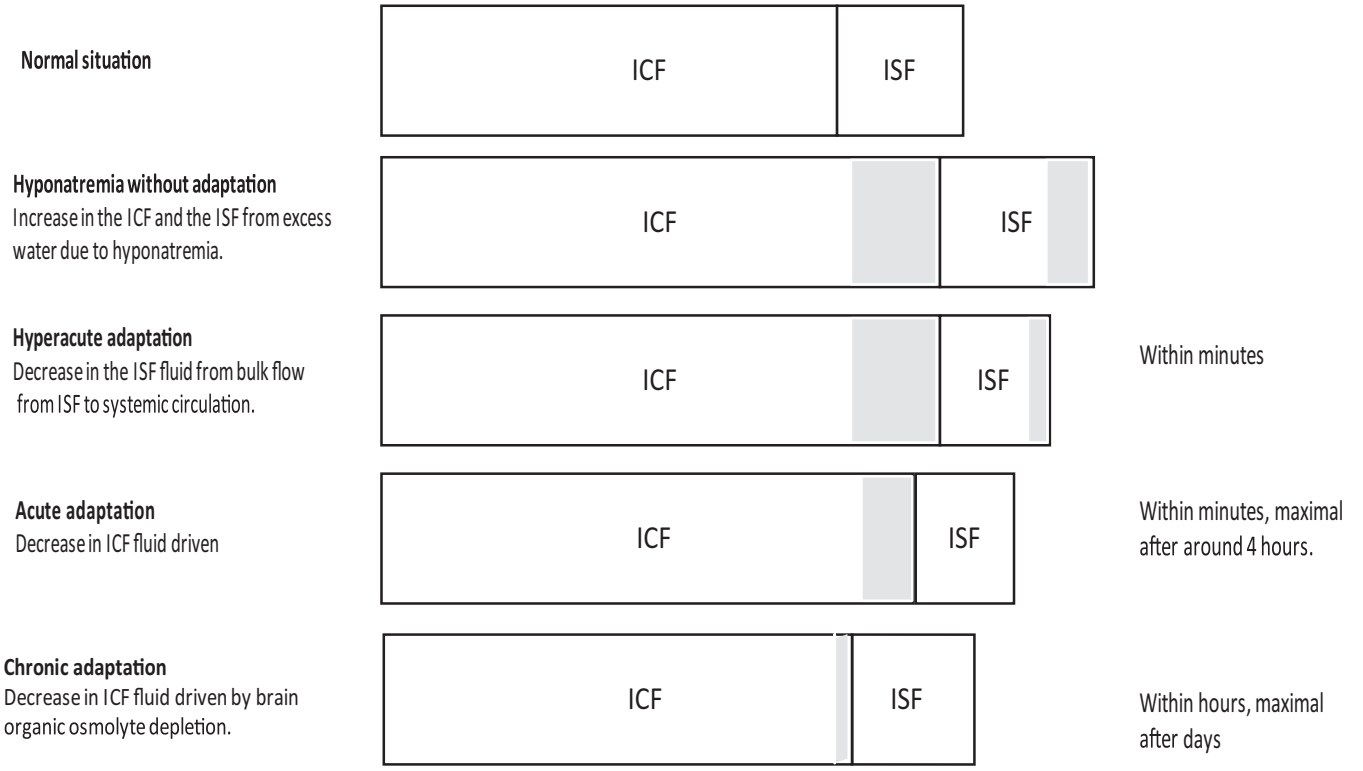

Figure 1. Mechanisms of brain adaptation to hyponatremia. Hyponatremia induces an increase in the intracellular fluid (ICF) and interstitial fluid (ISF). During hyperacute adaptation, water moves from the ISF compartment to systemic circulation. In the following hours, the depletion of intracellular electrolytes and nonelectrolyte osmolytes is responsible for the movement of water from the intracellular space in the extracellular space and later into the systemic circulation. This will ultimately decrease the brain water content. Adapted from Sterns, RH. The management of symptomatic hyponatremia. *Semin Nephrol.* 1990;10:503–514,[42] with permission from Elsevier.

limited nature of the electrolyte depletion of the brain, it is excepted that by the time the mechanisms behind electrolyte loss are exhausted, severe continued hyponatremia will inevitably cause significant brain edema. There are 2 pieces of evidence here to consider. On the one hand, it has clearly been shown experimentally and observed in clinical practice that the occurrence of severe hyponatremia within few hours will cause death from brain swelling.[36] (One of the first reports of evidence of brain edema secondary to hypo-osmolality occurred in a patient who underwent proctoclysis after an uneventful cholecystectomy who started to develop severe neurological symptoms 12 hours after the surgery and later succumbed from brain edema.[37]) On the other hand, when hyponatremia develops slowly, experimentally and in humans, even to a level of <100 mEq/l, there is no brain edema or immediately increased mortality.[38] This apparently contradictory evidence can be reconciled if one considers that there are other mechanisms, not yet active during acute hyponatremia, that help to prevent brain edema when hyponatremia becomes chronic.

Late Mechanisms of Brain Adaptation to Chronic Hyponatremia

It has been shown that after 4 days of hyponatremia, the brain electrolyte content in rats is reduced by 33%, 11%, and 17% for chloride, sodium, and potassium, respectively, but the brain water content only increases by 0.6%.[38] The loss of electrolytes during chronic severe hyponatremia does not account for the magnitude of the brain water changes. In other words, the absence of brain edema or the minimal increase in brain water content, despite excessive depletion of ionic electrolytes, suggest that the brain does not behave as a perfect osmometer during chronic hyponatremia. This shows that other osmotically active substances must be taken into account when explaining the minimal brain water changes during chronic hyponatremia. Studies in the early 1990s confirmed that organic osmolytes play a significant role in brain volume regulation during chronic hyponatremia. The importance of organic osmolyte is already evident even after 24 hours.[39–41] Quantitatively, it has been shown that the contribution of electrolytes in brain volume regulation in humans during chronic hyponatremia is approximately 70%, with the remaining 30% as the contribution of organic osmolyte loss.[42] Many of the identified organic osmolytes that are lost during chronic hyponatremia also play a role in vital cell functions such as neurotransmission and protein-folding pathways; therefore, their depletion might not be inconsequential and could be related to the neurological abnormalities observed in patients with chronic "asymptomatic" hyponatremia. It is now clear that osmolytes that are lost during chronic hyponatremia reaccumulate upon correction of hyponatremia. At least 2 studies have shown that the reaccumulation of electrolytes occurs faster with correction of hyponatremia, whereas organic osmolytes take much longer (>5 days) to return to baseline levels.[43,44] This observation carries weight because some have suggested that this delayed reaccumulation of organic osmolytes might play a role in the pathophysiology of osmotic demyelination syndrome.[45]

HYPONATREMIC ENCEPHALOPATHY

Hyponatremic encephalopathy (HNE) refers to the neurological dysfunction observed during hyponatremia. The clinical manifestations of HNE are related to the brain adaptation capacities to a hypo-osmotic challenge.

Risk Factors for HNE

The clinical manifestations of HNE are dependent on several factors, including the cause and the magnitude of hyponatremia, sex, age, and rapidity of onset.

The clinical picture of HNE resulting from acute hyponatremia might be different from the symptoms brought on by chronic hyponatremia. Acute hyponatremia with the same magnitude as chronic hyponatremia is likelier to induce more drastic symptoms, such as seizures or coma. During acute hyponatremia, when brain electrolyte content has reached its maximal point of depletion (~18%), and if organic osmolyte extrusion is not yet complete, brain edema will invariably occur. Clinically, this situation will happen if the SNa drops over a short period of time by a large magnitude. One study reported that if the rate of SNa decrease is <0.5 mEq/l per hour over 24 hours, then the clinical course is likely to be uncomplicated, whereas neurological sequalae and death are more common if the rate of sodium drop is >1 mEq/l per hour.[46]

HNE is more severe in preadolescents. This simply reflects the fact that most of the dramatic symptoms of HNE are related to brain edema.[47,48] The brain reaches it maximal size by 6 years of age, which is approximately 10 years earlier than the skull, which reaches its maximal size by 16 years of age. Therefore, during hyponatremia, brain edema will be more pronounced in younger individuals because their skulls pose more steric constraints than in adults.

The role of sex in HNE remains unclear. Experimental *in vitro* studies suggested that estrogens might affect astrocyte brain volume regulation,[49] but *in vivo* studies in rodents did not confirm that there was a different susceptibility to hyponatremia with regard to sex.[50,51]

The clinical data regarding female predisposition to HNE are also conflictual because the initial studies by Ayus *et al*. pointed to a female susceptibility,[52,53] but a large review did not confirm these findings.[54]

Hypoxia is undoubtedly a worsening factor in HNE; this has been documented by experimental and clinical studies.[55,56] The relationship between hyponatremia and hypoxia is complex. Swelling of the brain parenchyma compresses the brain vasculature and contributes to brain hypoxia that will cause neurogenic pulmonary edema, which, in turn, will reduce oxygen delivery to the brain.[57] However, others have shown that the occurrence of severe systemic hypoxia in the setting of severe acute hyponatremia itself is uncommon.[58]

Symptoms of HNE

The most striking and severe symptoms of HNE are related to the compression of the brain parenchyma against the rigid skull. In severe cases, brain herniation and death often occurs preceded by seizures and coma.[59] As discussed earlier, these symptoms often occur during acute and profound hyponatremia because the brain has no or little time to adjust to hypoosmolality. Severe symptoms can also occur after acute on chronic hyponatremia, or even after moderate acute hyponatremia. For instance, marathon runners with moderate hyponatremia were reported to experience nausea and vomiting, and sometimes acute confusion, which were treated effectively by correction of SNa.[60] The largest series of patients studied with HNE revealed that acute severe hyponatremia might be fatal, with abrupt respiratory arrest in up to 60% of cases, but prompt reversal of the prognosis can occur with correction of SNa.[61]

Chronic hyponatremia will usually manifest as malaise, weakness, and confusion.[62] Until the last decade, it was believed that mild chronic hyponatremia was asymptomatic and carried little neurological dysfunction. Studies by our team and others revealed that chronic hyponatremia is associated with significant subtle neurological abnormalities, including attention deficit, falls, and gait imbalance. Patients with chronic hyponatremia have a much higher risk of falls, which seems to more marked in older adult patients.[63,64] Some of these manifestations are reversible upon improvement in SNa.[63–66] Table 1 shows the manifestations of HNE.

The physiological basis of chronic HNE is starting to be elucidated. One group recently demonstrated that the extracellular glutamate content in chronic hyponatremic rats was increased, and that the astrocytic glutamate uptake in low sodium medium was also unpaired.[67] These results are consistent with the fact that glutamate is a significant organic osmolyte that is extruded from the cell. Because other osmolytes have important functions in brain physiology (e.g., taurine was studied as anticonvulsant in rats), it is likely that the brain depletion of these organic osmolytes might play a role in HNE.

Table 1. Manifestations of hyponatremic encephalopathy

Acute severe	Chronic
Nausea and vomiting	Nausea
Headaches	Fatigue
Seizures	Gait and attention deficit
Coma	Falls and bone fractures
Death	
Respiratory arrest	
Noncardiogenic pulmonary edema	

Treatment of HNE

Severe HNE

The criteria for severe HNE includes altered mental status, seizures, focal neurological damage, coma, and other signs or symptoms of brain herniation. Severe HNE is a medical emergency and the treatment should be undertaken promptly. Chronic hyponatremia, if not complicated by an acute episode, rarely presents as severely symptomatic HNE. To date, few life-threatening manifestations have been associated with chronic hyponatremia even if severe; this reflects the almost completed adaptation of the brain during chronic hyponatremia with a negligible brain volume increase.

In all cases, the treatment should aim to reverse severe neurological manifestations that the clinician believes to be secondary to hyponatremia. Therefore, prompt correction of hyponatremia should be undertaken in patients who present with severe symptoms, regardless of the chronicity and the magnitude of the decrease in SNa.[68,69]

The mainstay of treatment of HNE is the reduction of intracranial pressure by decreasing brain water content. The neurosurgery literature has suggested that in normonatremic patients with others causes of brain edema, an increase in the plasma sodium of approximately 5 to 6 mEq/l is sufficient to decrease the intracranial pressure by 5 to 10 mm Hg, which would prevent brain herniation.[70–72] Based on these findings, it could be postulated that a similar increase in SNa in patients with hyponatremia would be enough to reduce intracranial pressure to nonlife-threatening levels. This can be achieved by rapid infusion of hypertonic saline. The suggested dose and administration scheme varies according to the different guidelines, but it is well accepted that boluses of 100 to 300 ml of 3% sodium chloride are effective. It should be remembered that the boluses must be repeated until symptoms of brain edema regress. Importantly, frequent sodium monitoring is mandatory.

It has recently been shown that a single dose of enteral urea (15 g) urea can decrease intracranial pressure by up to 8 mm Hg in neurotrauma patients with an intracranial pressure of >15 mm Hg.[73]

Moderate HNE

The treatment options for mild and moderate HNE depend on the cause of hyponatremia. The cornerstone of treatment is to adjust the numerator or the denominator of Edelman's equation to restore normal SNa concentrations. In patients with salt depletion from renal or extrarenal causes, replacement of salt stock will normalize SNa. This could be achieved with normal saline infusion or oral salt tablets for salt-depleted patients. Patients with syndrome of inappropriate antiduiretic hormone secretion who have excessive total body water could benefit from water restriction and aquaretics such as V2 receptors antagonist or urea.

Brain Complications Following Treatment of Hyponatremia

Rapid correction of chronic hyponatremia can sometimes lead to neurological damage. From the late 1950s to the early 1970s, several authors described case reports of hyponatremic alcoholic patients who died during treatment and who had necropsy findings consistent with central pontine myelinolysis (CPM). It was not clear at that time if SNa levels *per se* or if it was rather the correction of serum sodium that was the cause of the neurological deterioration.[74–76] The most definitive evidence of the relationship between correction of chronic hyponatremia and CPM came from experimental studies that showed significant demyelination in rats, rabbits, and dogs after rapid correction of chronic hyponatremia.[77–79] Sterns *et al*.[80–82] studied patients with severe hyponatremia and found that permanent neurological damage occurred only in patients who had their hyponatremia corrected too rapidly. That publication contrasted with a previous study by Arieff[56] who suggested that either acute or chronic hyponatremia should be corrected rapidly to avoid permanent neurological damage.[56] The demyelination seen after correction of chronic hyponatremia is now called osmotic demyelination syndrome (ODS). CPM is a more generic term that reflects the loss of myelin in the pons. CPM occurs in several other conditions aside from rapid correction of chronic hyponatremia, and ODS can also affect extrapontine regions. The experimental model of ODS has shed light on the pathophysiology of the disorder.[83–91]

ODS is a rarely reported disorder because the disease is rare; however, there is also a possibility that the reporting rate might be lower than the actual prevalence rate because some clinicians might be reluctant to report a potentially preventable complication of hyponatremia treatment. It is also possible that some cases of ODS[92,93] can be clinically silent, and total recovery has been described in some patients.

Risk Factors for ODS

Some risk factors have been associated with development of ODS, but due to the rare nature of the disease, they have not been studied systematically. The most important predisposing factors for ODS are the chronicity of hyponatremia and the final increment of SNa achieved over 24 hours. It is now believed that the 24-hour sodium increment as opposed to the hourly increment of SNa is more important.[94,95] Other risk factors include malnutrition, liver disease, and alcoholism.[96] Hypokalemia has also been mentioned in some reports but has not been studied experimentally.[97] It should be mentioned that the correction of hypokalemia might increase SNa as predicted by Edelman's equation. ODS is seldom seen in patients with acute hyponatremia, and experimental evidence has shown that chronicity of hyponatremia is an important prerequisite.[98] One of the explanations might be that during acute hyponatremia, the loss of organic osmolytes is less important because they seem to play a protective role in the development of the disease.[45]

Over the last 4 decades, the cutoff of the sodium increment in 24 hours, at which the correction of chronic hyponatremia is deemed safe, has varied significantly (reviewed by Martin[96]). The largest series reported in experimental research that addressed the topic of threshold for demyelination lesions revealed that no animal had clinical evidence of neurological impairment of displayed myelin loss at a cutoff of 16 mEq/l per 24 hours.[95] However, it should be noted that clinical manifestations of neurological disturbance are difficult to appreciate in animals, and these early experiments did not use the most sensitive techniques for determination of myelin damage. In clinical practice, it is believed that increments of <8 to 10 mEq/l per day are nevertheless associated with low risk of significant symptoms from ODS if there is no concomitant hypokalemia or alcoholism. Although there are still some case reports that describe a diagnosis of ODS after correction of SNa with an increment of <10 mEq/l per 24 hours over a 24-hour period,[99,100] the real increment of SNa might have been underscored because the SNa before the hospital admission and before the initiation of correction is often unknown. Therefore, some patients could have started to self-correct their hyponatremia before they presented to the hospital, which made their real sodium levels higher than reported.

Mechanisms of ODS

Several factors contribute to the apparition of demyelinative brain lesions upon correction of chronic hyponatremia. It was initially suggested that BBB

breakdown allowed invasion of the brain parenchyma with myelinolytic substances, including cytokines and complement factors.[90] Microglial activation was also suggested to play a role.[87,88] Recent reports clearly established that one of the first events after rapid correction of chronic hyponatremia is astrocyte damage.[83] It was further demonstrated that rapid correction of chronic hyponatremia induces protein aggregation in astrocytes, together with unfolded protein response and an exaggerated endoplasmic reticulum stress that will culminate into astrocyte death.[85] These events occur before any histological evidence of myelin damage, and they all take place in regions prone to demyelination. The relationship between astrocyte death and myelin breakdown is explained by the fact that astrocytes provide trophic support to oligodendrocytes, and astrocytes are required for maintenance of normal myelin. Figure 2 illustrates the current knowledge on the pathophysiology of the disease.

Prevention of Brain Edema and Avoidance of ODS in the Treatment of HNE

Strategies to minimize the risk of ODS while treating severe HNE should focus on several goals: (i) identification of patients who need rapid correction of hyponatremia; (ii) identification of patients at risk of ODS; and (iii) minimizing the increment of SNa and achieving the necessary increment to reverse the life-threatening manifestations of HNE (Figure 3).

Depending on the cause of hyponatremia, an increase in SNa can be achieved using several therapeutic agents, including hypertonic saline, normotonic saline, diuretics, urea, or V2 receptor antagonists. The rapidity of onset, the reversibility and the duration of the effect might be different for these agents. For example, hypertonic saline will produce a more brisk increment of SNa than normal saline or urea, and treatment with V2 receptor antagonists could produce a long lasting aquaresis and brisk correction of SNa depending on the half-life and the dose of the chosen agent. Experimental evidence has suggested that the use of urea is less prone to induce ODS compared with hypertonic saline and vaptans.[84] It was found that animals treated with urea had minimal experimental demyelinative lesions despite an increment of >25 mEq/l per 24 hours. A follow-up study confirmed that urea decreased the unfolded protein response and endoplasmic reticulum stress in the brain after correction of hyponatremia.[85]

The recommended scheme for severely symptomatic hyponatremia includes administration of hypertonic saline (100 ml boluses of sodium chloride 3%) until symptoms abate. Patients who need urgent correction of SNa, as mentioned previously, are patients who present with severe symptoms related to brain edema. Although to date no study has looked at the net brain volume decrease brought on by a given increment of SNa, in neurosurgery patients with normonatremia and impending brain herniation from trauma or brain

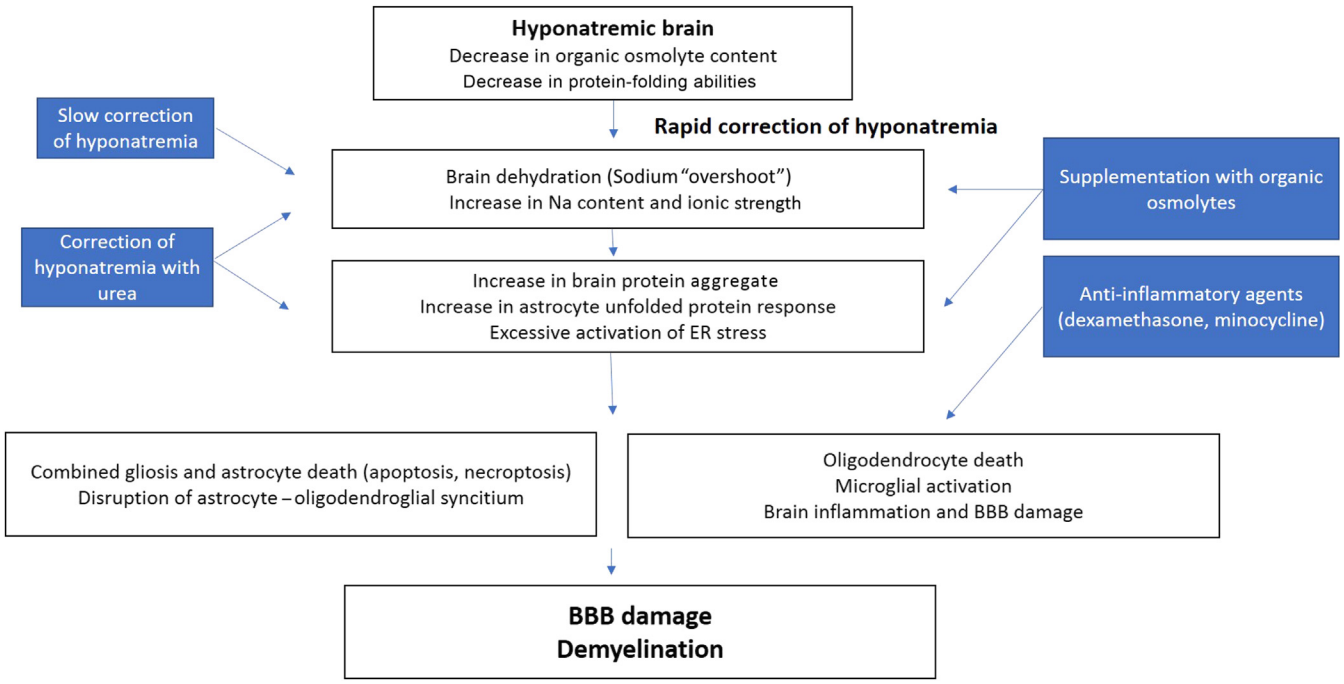

Figure 2. Schematic representation of the pathophysiology of osmotic demyelination after rapid correction of chronic hyponatremia. Therapeutic approaches are depicted in the blue boxes. BBB, blood–brain barrier; ER, endoplasmic reticulum.

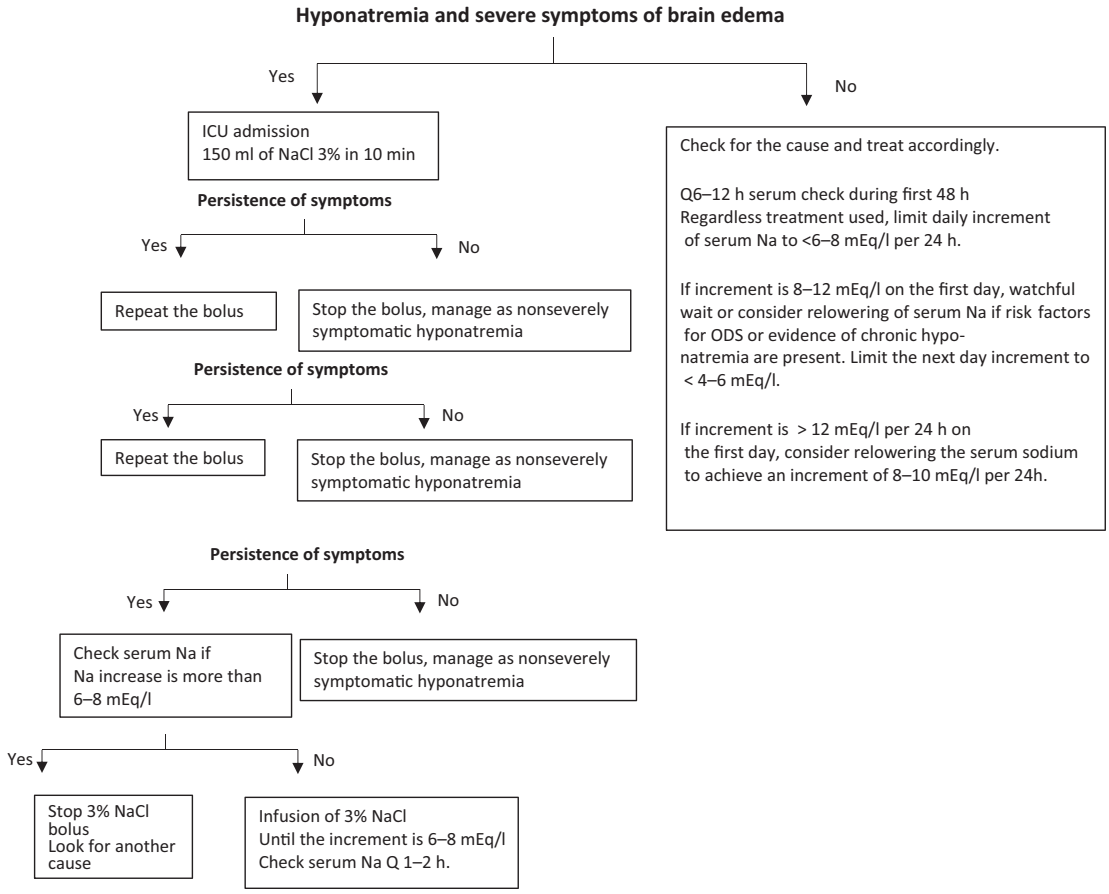

Figure 3. Proposed algorithm for the management of hyponatremia with regard to central nervous system. This algorithm is given as a first basis for management and should integrate the particularities of each patient. The most important parameter in determining the need of urgent treatment should be the presence of neurological symptoms attributable to hyponatremia and not the chronicity of hyponatremia or the magnitude of hyponatremia. Chronic hyponatremia with limited neurological symptoms is a risk factor for osmotic demyelination syndrome (ODS) and dictates slow correction of serum sodium, regardless the correction method selected. Acute hyponatremia with no neurological symptoms should not be corrected rapidly because there are many caveats in the evaluation of the duration of hyponatremia, and little is known about the duration that poses a risk for ODS. These limits are based on the current state of the literature, but unpublished evidence suggests that the lower increment is the better. ICU, intensive care unit; Na, sodium; NaCl, sodium chloride.

tumor, increasing SNa to approximately 5 to 6 mEq /l is sufficient to lower the intracranial pressure by approximately 10 to 15 mm Hg and prevent brain herniation.[70,72] Therefore, it could be speculated that such a small increment of SNa might be enough to stop the symptoms of brain edema associated with hyponatremia. Sterns *et al*. have proposed that the SNa should not be corrected by >6 mEq/l in the first 24 hours.[101] To date, there are no experimental data or large clinical data to support this recommendation, and experimental studies are still needed to determine if correction of SNa by >6 mEq/l and <10 mEq/l is associated with some neurological impairment.

Accumulating evidences have supported the experimental findings[102–105] that relowering of SNa could prevent or mitigate the disease when rapid correction has been undertaken.[106] Relowering of SNa should ideally be performed within 12 to 24 hours of overcorrection and can be achieved using 1-desamino-8-d-arginine vasopressin and dextrose infusion.[106] Controlled increased of SNa can be performed by combining 1-desamino-8-d-arginine vasopressin infusion along with hypertonic saline.[101,107]

CONCLUSION AND FUTURE PERSPECTIVES

The regulation of body fluid osmolality is of a crucial importance, and throughout evolution, this property has been conserved in fish to mammals. The cell volume and macromolecular crowding, and hence, essential biological functions are closely dependent on extracellular tonicity.

Despite being the most common electrolyte disorder in clinical practice, the treatment of hyponatremia still represents a challenge for the clinician, and this has not changed much since back in the 1990. Berl summarized this conundrum by the famous phrase: "Treating hyponatremia, damned if you do and damned if you don't."[108] If severe and of rapid onset, hyponatremia could induce brain edema with

potentially lethal consequences. Mild to moderate hyponatremia has also been associated with various degrees of neurological dysfunction. In contrast, rapid correction of chronic hyponatremia is linked to brain demyelination.

To date, although experimental findings have suggested potential benefit in treating mild hyponatremia on outcomes such as gait and memory,[67] there have been no large-scale clinical data suggesting that the treatment of mild to moderate hyponatremia is associated with a better neurological outcome.

Despite the significant amount of research on the topic, there are still several areas of uncertainty, and there is a crucial need of more studies to answer the following questions: How does the brain sense hyponatremia? What is the minimal increment of SNa that will safely prevent brain edema in a severely symptomatic hyponatremia patient, and conversely, how much of an increment of SNa poses a risk of brain damage from ODS? What is the role of the vasopressin receptor antagonist in the prevention of neurological complications of hyponatremia? Hopefully, future research will help to address these issues.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This work was supported by a grant from FNRS Grant number J0137.14 and a grant from the Fondation Erasme. The authors are indebted to Bruno Couturier and Alain Soupart for their helpful revision of this manuscript. The authors would like to apologize to those researchers whose work could not be cited due to space limitations.

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