CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Electrolyte Disorders in Community Subjects: Prevalence and Risk Factors

George Liamis, MD, PhD[a] Eline M. Rodenburg, MD, PhD[a,b] Albert Hofman, MD, PhD[a] Robert Zietse,[c] Bruno H. Stricker, PhD,[a,b] Ewout J. Hoorn, MD, PhD[c]

[a]Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands; [b]Drug Safety Unit, Inspectorate of Health Care, The Hague, The Netherlands; and [c]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands.

ABSTRACT

BACKGROUND: Electrolyte disorders have been studied mainly in hospitalized patients, whereas data in the general population are limited. The aim of this study was to determine the prevalence and risk factors of common electrolyte disorders in older subjects recruited from the general population.

METHODS: A total of 5179 subjects aged 55 years or more were included from the population-based Rotterdam Study. We focused on hyponatremia, hypernatremia, hypokalemia, hyperkalemia, and hypomagnesemia. Multivariable logistic regression was used to study potential associations with renal function, comorbidity, and medication. The adjusted mortality also was determined for each electrolyte disorder.

RESULTS: A total of 776 subjects (15.0%) had at least 1 electrolyte disorder, with hyponatremia (7.7%) and hypernatremia (3.4%) being most common. Diabetes mellitus was identified as an independent risk factor for hyponatremia and hypomagnesemia, whereas hypertension was associated with hypokalemia. Diuretics were independently associated with several electrolyte disorders: thiazide diuretics (hyponatremia, hypokalemia, hypomagnesemia), loop diuretics (hypernatremia, hypokalemia), and potassium-sparing diuretics (hyponatremia). The use of benzodiazepines also was associated with hyponatremia. Hyponatremic subjects who used both thiazides and benzodiazepines had a 3 mmol/L lower serum sodium concentration than subjects using 1 or none of these drugs ($P < .001$). Hyponatremia and hypomagnesemia were independently associated with an increased mortality risk.

CONCLUSIONS: Electrolyte disorders are common among older community subjects and mainly associated with diabetes mellitus and diuretics. Subjects who used both thiazides and benzodiazepines had a more severe degree of hyponatremia. Because even mild electrolyte disorders were associated with mortality, monitoring of electrolytes and discontinuation of offending drugs may improve outcomes.

 • *The American Journal of Medicine (2013) 126, 256-263*

KEYWORDS: Benzodiazepines; Diabetes mellitus; Diuretics; Epidemiology; Hyponatremia

Electrolyte disorders are common in hospitalized patients and associated with increased morbidity and mortality. Although it has been difficult to distinguish whether this adverse outcome is directly related to the electrolyte disorder or the underlying disease, a number of recent studies favor the former.[1-5] In hospitalized patients, electrolyte disorders are often acute and severe, which may explain poorer outcomes. In recent years, however, it has become clear that chronic and mild electrolyte disorders also are associated with adverse outcomes, including in the general population.[1,4-7] Because of these emerging insights, it is important to know the exact prevalence and risk factors of electrolyte disorders in the general population. To date, limited work has been performed on the epidemiology of electrolyte disorders in community-dwelling subjects. Therefore, our objective was to study the prevalence of, and risk factors for, electrolyte disorders in subjects recruited from the general population. We focused on 5 clinically significant electrolyte disorders, including hyponatremia, hypernatremia, hypokalemia, hyperkalemia, and hypomagnesemia. Hyponatremia and hypernatremia are primarily water balance

Funding: None.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

Requests for reprints should be addressed to Bruno H. Stricker, MB, PhD, PO Box 2040, 3000 CA Rotterdam, The Netherlands.

E-mail address: b.stricker@erasmusmc.nl

0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2012.06.037

disorders and therefore usually caused by perturbations in the antidiuretic hormone vasopressin. Hypokalemia and hyperkalemia are often related to increased or reduced activity of the renin angiotensin system; poor dietary intake and gastrointestinal potassium loss also may contribute to hypokalemia. Hypomagnesemia is usually the result of renal or gastrointestinal magnesium loss. The analysis of these electrolyte disorders was performed in the Rotterdam Study cohort for 2 reasons: the Rotterdam Study has elaborate information on comorbidity and medication, which are the most common causes of electrolyte disorders; and the participants in this cohort were aged 55 years or more, which constitutes a population at risk for electrolyte disorders.[8]

CLINICAL SIGNIFICANCE

- Mild electrolyte disorders are common in the general population aged 55 years or more (15%).
- Risk factors for electrolyte disorders in the general population are similar to those in hospitalized patients, including diabetes mellitus and all types of diuretics.
- Benzodiazepines were associated with hyponatremia, and subjects who used both thiazides and benzodiazepines had more severe hyponatremia than those using thiazides or benzodiazepines alone.

MATERIALS AND METHODS

Study Population

This study was conducted within the framework of the Rotterdam Study, an ongoing prospective, population-based cohort study among subjects aged 55 years or more, living in Ommoord, a suburb of Rotterdam, The Netherlands. The rationale and design of the Rotterdam Study have been described.[9] Briefly, all 10,275 inhabitants were invited for baseline examination between August 1990 and June 1993. Of those, 7983 participated. For the current study, we analyzed a total of 5179 participants for whom data on serum sodium, potassium, and magnesium were present at baseline. Significant differences between included and excluded participants were as follows: age (70.3 vs 71.2 years, $P < .001$), current smoking (23.8% vs 20.3%, $P < .001$), hypertension (34.9% vs 38.9%, $P = .002$), and use of potassium-sparing diuretics (1.5% vs 2.1%, $P = .038$). The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, and written informed consent was obtained from all participants.

Electrolyte Measurements

Serum sodium, potassium, and magnesium were measured at baseline within our clinical chemistry department using standard methods. The definitions of the electrolyte disturbances, based on the cutoff used in our laboratory, were as follows. Hyponatremia was defined as a serum sodium concentration less than 136 mmol/L, and hypernatremia was defined as a serum sodium concentration greater than 145 mmol/L. Hypokalemia was defined as a serum potassium concentration less than 3.5 mmol/L, and hyperkalemia was defined as a serum potassium concentration greater than 5.3 mmol/L. Finally, hypomagnesemia was defined as a serum magnesium concentration less than 0.65 mmol/L. Serum sodium was not corrected for serum glucose because few participants had a degree of hyperglycemia that could explain their hyponatremia.

Risk Factors

Body mass index (BMI) and renal function, and the comorbidities type 2 diabetes mellitus, hypertension, and heart failure were selected as potential risk factors for electrolyte disorders. BMI was calculated as weight in kilograms divided by height in centimeters squared. Creatinine and nonfasting glucose levels were measured at baseline within our clinical chemistry department using standard methods. Baseline renal function was assessed by calculating the estimated glomerular filtration rate using the 4-variable Modification of Diet in Renal Disease formula and was expressed in milliliters/minute/1.73 meters squared.[10]

The presence of type 2 diabetes mellitus was defined by the current use of antidiabetic medication or by a nonfasting or post-load plasma glucose level greater than 11.1 mmol/L (200 mg/dL). Hypertension was defined as a systolic blood pressure of 160 mm Hg or more, a diastolic blood pressure of 100 mm Hg or more, or current use of antihypertensive medication.[11] Assessment of prevalent heart failure at the baseline examination in the Rotterdam Study has been described in detail.[12] The following types of drugs were selected as potential risk factors for electrolyte disorders: diuretics classified as loop, thiazide, and potassium-sparing diuretics (Anatomical Therapeutic Chemical [ATC] code C03), anti-epileptics (ATC code N03), psycholeptics (ATC code N05; benzodiazepines, phenothiazines, butyrophenones), and psychoanaleptics (ATC code N06; antidepressants, psychostimulants, and antidementia drugs). The use of medication was determined by questionnaire at baseline. Drug exposure (classified by ATC code [http://www.whocc.no/atc_ddd_index/]) is continuously being monitored since the initiation of the Rotterdam Study in 1991 by using computerized pharmacy records of the pharmacies in the Ommoord district. Because many baseline interviews were taken before 1991, we used only questionnaire data.

Mortality

Data on all-cause mortality were obtained by continuous monitoring of the municipal address files. Vital status was set at the reference date (for participants living in the area of Ommoord) or at the last date of manual data collection (for

participants living outside Ommoord or in a nursing home). Follow-up information was used up to January 1, 2008.

Statistical Analysis

The prevalence of electrolyte disorders was determined by frequency analyses at baseline. Multivariable logistic regression analysis was used to study associations between the predefined risk factors and the electrolyte disorders. This was done using linear regression analyses adjusted for age, sex, BMI, estimated glomerular filtration rate, and the predefined comorbidities and medications. A subanalysis was performed to assess the combination of drug effects within hyponatremic subjects using 1-way analysis of variance followed by a post hoc test. Cox proportional hazard models were used to analyze the association between electrolyte disorders and mortality. These analyses were adjusted for sex and age in the first model, and for sex, age, BMI, estimated glomerular filtration rate, diabetes mellitus, prevalent heart failure, and previous myocardial infarction in the second model. All analyses were performed using the Statistical Package for the Social Sciences version 15.0 (SPSS Inc, Chicago, Ill). A P value less than .05 was considered statistically significant.

RESULTS

Baseline Characteristics

The baseline characteristics of the study population are shown in **Table 1**. Of note, many subjects had hypertension and used diuretics or psycholeptics. Of the subjects using psycholeptics, the majority used benzodiazepines (96%), whereas a small minority used phenothiazines or butyrophenones (4%). Therefore, subsequent analyses were performed with benzodiazepines only.

Table 1 Baseline Characteristics, Comorbidity, Medication, and Electrolyte Disorders of the Study Population

	Total Population (n = 5179)
General characteristics	
Women, n (%)	3188 (61.6)
Age, y (± SD)	70.27 ± 9.13
BMI, kg/m^2 (± SD) (n = 5038)*	26.27 ± 3.75
eGFR (mL/min/1.73 m^2)	74 ± 16
Comorbidity	
Current smoking, n (%) (n = 4997)*	1191 (23.8)
Diabetes mellitus at baseline, n (%) (n = 5147)*	563 (10.9)
Hypertension at baseline, n (%) (n = 5094)*	1780 (34.9)
Heart failure at baseline, n (%)	176 (3.4)
Medication	
Use of thiazide diuretics, n (%)	560 (10.8)
Use of loop diuretics, n (%)	281 (5.4)
Use of potassium-sparing diuretics, n (%)	77 (1.5)
Use of psycholeptics, n (%) (n = 3782)*	816 (21.5)
Of which benzodiazepines, n/total (%)	784 (20.7)
Use of psychoanaleptics, n (%) (n = 3782)*	115 (3.0)
Use of antiepileptics, n (%) (n = 3782)*	68 (1.8)

BMI = body mass index; eGFR = estimated glomerular filtration rate; SD = standard deviation.
*Indicates the number of subjects in whom these data were available (only shown when different from total population).

Prevalences

The prevalences for each of the electrolyte disorders are shown in **Table 2**. Hyponatremia and hypernatremia were the most common electrolyte disorders, whereas hyperkalemia was relatively uncommon. Significant interactions between increasing age and the prevalence of hyponatremia and hyperkalemia were found. Compared with normonatremic subjects, subjects with hyponatremia (73.4 ± 10.3 years vs 70 ± 8.9 years, $P = .001$) and hyperkalemia (80.5 ± 7.3 years vs 70.2 ± 9.1 years, $P < .001$) were older compared with controls. Hypokalemia was approximately 2 times more often present in women (3.5% vs 1.5%, $P < .001$). Overall, 776 subjects (15.0%) had at least 1 electrolyte disorder.

Risk Factors for Electrolyte Disorders

Table 3 shows which of the predefined risk factors were associated with hyponatremia, hypernatremia, hypokalemia, or hypomagnesemia. Associations between potential risk factors and hyperkalemia were not analyzed because this group was too small. Of the comorbidities studied, diabetes mellitus was associated with hyponatremia and hypomagnesemia (odds ratio [OR], 1.98; 95% confidence interval [CI], 1.47-2.68 and OR, 3.32; 95% CI, 2.00-5.50, respectively), whereas hypertension was associated with hypokalemia (OR, 2.73; 95% CI, 1.68-4.42). With regard to medication, diuretics were associated with several electrolyte disorders. Thiazide diuretics were associated with hyponatremia, hypokalemia, and hypomagnesemia. Loop diuretics were associated with hypernatremia and hypokalemia. Potassium-sparing diuretics were associated with hyponatremia. Other types of drugs were mainly associated with hyponatremia, including antiepileptics and benzodiazepines. Logistic regression analyses showed that the presence of diabetes mellitus (OR, 1.63; 95% CI, 1.28-2.09), hypertension (OR, 1.23; 95% CI, 1.00-1.50), and BMI (OR, 0.95; 95% CI, 0.95-1.00) were associated with the presence of at least 1 electrolyte disorder. In regard to drug use, the use of antiepileptics (OR, 2.22; 95% CI, 1.23-4.00), loop diuretics (OR, 1.65; 95% CI, 1.14-2.40), thiazides (OR, 2.40; 95% CI, 1.87-3.09), or potassium-sparing diuretics (OR, 2.21; 95% CI, 1.26-3.87) was associated with the presence of at least 1 electrolyte disorder. The prevalence of at least 1 electrolyte disorder was 18.7% in diabetic patients, 25.7% in subjects taking diuretics, and 36.3% in diabetic patients taking diuretics. The majority of subjects with hypokalemia used diuretics (59.7%), and the prevalence of hypokalemia was higher in subjects using diuretics (6.5% in subjects using thiazides, 3% in subjects using loop diuretics, and 1.1% in subjects not using diuretics).

Table 2 Prevalence of Selected Electrolyte Disorders in the General Population by Age

Electrolyte Disorder*	Prevalence n/5179 (%)	Mean ± SD	Range	More Severe Degree, n (%)†	*P* Value
Hyponatremia					<.001
55-64 y	105 (6.1)	133.3 ± 2.1	125-135	6 (5.7)	
65-74 y	112 (5.9)	133.6 ± 2.0	124-135	5 (4.5)	
≥75 y	180 (11.6)	133.1 ± 2.1	126-135	13 (7.2)	
Hypernatremia					.6
55-64 y	64 (3.7)	148.0 ± 3.1	146-160	10 (15.6)	
65-74 y	59 (3.1)	148.1 ± 3.0	146-157	10 (16.9)	
≥75 y	54 (3.5)	147.6 ± 2.3	146-159	5 (9.3)	
Hypokalemia					.14
55-64 y	38 (2.2)	3.35 ± 0.14	3.00-3.49	0 (0)	
65-74 y	52 (2.7)	3.32 ± 0.17	2.40-3.49	1 (1.9)	
≥75 y	52 (2.3)	3.31 ± 0.18	2.70-3.49	3 (5.8)	
Hyperkalemia					<.001
55-64 y	0 (0)	0 (0)	NA	0 (0)	
65-74 y	3 (0.2)	5.44 ± 0.12	5.30-5.51	0 (0)	
≥75 y	11 (0.7)	5.48 ± 0.19	5.30-5.87	0 (0)	
Hypomagnesemia					.36
55-64 y	41 (2.4)	0.63 ± 0.03	0.49-0.65	1 (2.4)	
65-74 y	33 (1.7)	0.63 ± 0.02	0.56-0.65	0 (0)	
≥75 y	30 (1.9)	0.61 ± 0.08	0.23-0.65	2 (6.7)	

NA = not available; SD = standard deviation.
*See "Materials and Methods" for definitions.
†Percentages represent the proportion of severe disorder within the group with the disorder; the following values were considered to represent more severe degrees of each electrolyte disorder: serum sodium < 130 mmol/L (for hyponatremia) and > 150 mmol/L (for hypernatremia); serum potassium < 3.0 mmol/L (for hypokalemia) and > 6.0 mmol/L (for hyperkalemia); and serum magnesium < 0.50 mmol/L (for hypomagnesemia).

Drug-induced Hyponatremia

Given the fact that hyponatremia was associated with several drugs, we assessed whether a combination of these drugs resulted in more severe hyponatremia. Indeed, we found that subjects receiving both thiazides and benzodiazepines had a significantly lower serum sodium (130.3 ± 2.8 mmol/L) compared with hyponatremic subjects who used only benzodiazepines (133.4 ± 1.8 mmol/L), only thiazides (132.8 ± 2.3 mmol/L), or none of these drugs (133.6 ± 1.9 mmol/L) (**Figure**). Linear regression analysis, adjusted for

Table 3 Risk Factors of Electrolyte Disorders in the Study Population

	Hyponatremia OR (95% CI)	Hypernatremia OR (95% CI)	Hypokalemia OR (95% CI)	Hypomagnesemia OR (95% CI)
Sex	0.89 (0.68-1.17)	1.05 (0.69-1.60)	1.96 (1.22-3.12)*	1.10 (0.66-1.83)
Age	1.02 (1.01-1.04)*	0.99 (0.97-1.01)	0.99 (0.96-1.01)	0.97 (0.95-1.00)
BMI	0.99 (0.95-1.02)	0.96 (0.91-1.01)	0.92 (0.87-0.97)*	1.02 (0.96-1.08)
eGFR	1.00 (0.99-1.01)	0.99 (0.98-1.01)	1.01 (0.99-1.02)	1.00 (0.99-1.02)
Diabetes mellitus	1.98 (1.47-2.68)†	0.84 (0.45-1.56)	1.11 (0.66-1.86)	3.32 (2.00-5.50)†
Hypertension	1.07 (0.82-1.39)	0.95 (0.62-1.44)	2.73 (1.68-4.42)†	1.04 (0.62-1.73)
Heart failure	1.06 (0.62-1.81)	0.65 (0.24-1.79)	1.17 (0.54-2.54)	1.00 (0.36-2.82)
Antiepileptics	2.98 (1.54-5.76)*	0.53 (0.07-3.88)	0.84 (0.11-6.35)	1.88 (0.44-8.06)
Benzodiazepines	1.43 (1.07-1.90)*	1.02 (0.64-1.64)	1.02 (0.63-1.63)	0.78 (0.41-1.47)
Psychoanaleptics	0.95 (0.45-2.02)	1.15 (0.40-3.25)	0.25 (0.03-1.93)	0.46 (0.06-3.45)
Thiazide diuretics	1.66 (1.18-2.33)*	1.05 (0.56-1.95)	7.68 (4.92-11.98)†	2.17 (1.19-3.96)*
Loop diuretics	1.27 (0.78-2.06)	2.59 (1.28-5.24)*	3.71 (1.85-7.44)†	1.61 (0.65-4.01)
Potassium-sparing diuretics	3.64 (1.94-6.82)†	1.07 (0.30-3.87)	—	2.33 (0.68-8.02)

BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; OR = odds ratio.
*$P < .05$.
†$P < .001$.

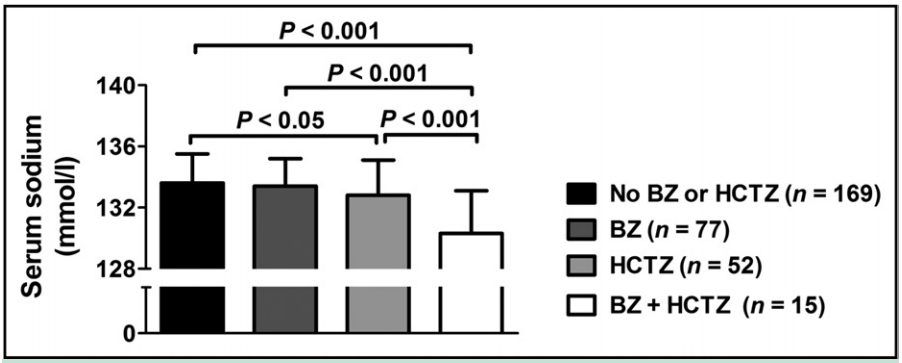

Figure 1 The analysis was performed by 1-way analysis of variance followed by a post hoc test. BZ = benzodiazepines; HCTZ = hydrochlorothiazide.

all covariables, showed similar results. A lower sodium level of −0.90 mmol/L (95% CI, −1.65 to −0.17) was observed in hydrochlorothiazide users, and a −3.14 mmol/L (95% CI, −4.28 to −2.00) lower sodium level was observed in hydrochlorothiazide users in combination with benzodiazepines. Other combinations of drugs associated with hyponatremia were not analyzed because of low numbers.

Outcomes

Table 4 shows the crude and adjusted mortality risks for each of the electrolyte disorders studied. Hyponatremia and hypomagnesemia were associated with an increased mortality risk (hazard ratios, 1.17 and 1.39, respectively), whereas this association disappeared for hyperkalemia when correcting for kidney function, the presence of diabetes mellitus, and cardiovascular status.

DISCUSSION

The principal results indicate that electrolyte disorders are common in community-dwelling subjects aged 55 years or more, with approximately 1 in 6 subjects having at least 1 electrolyte disorder. The water balance disorders hyponatremia and hypernatremia were most commonly observed. The prevalence of hyponatremia and hyperkalemia increased significantly with age (**Table 2**). Hyponatremia and hypomagnesemia were associated with a greater mortality risk (**Table 4**). Among subjects with hyponatremia, those using thiazides and benzodiazepines had a more severe degree of hyponatremia than subjects using 1 or none of these drugs (**Figure**). Overall, type 2 diabetes mellitus and diuretics were identified as the most important independent risk factors for electrolyte disorders (**Table 3**).

Our data regarding the prevalence of electrolyte disorders, and age and gender differences in electrolyte disorders, mainly confirmed previous observations. For example, a previous study also identified age as a risk factor for hyponatremia and reported a similar prevalence in the community (7.7%).[13] Two previous studies also showed that older women had a predisposition to hypokalemia,[14,15] possibly because of lower exchangeable body potassium due to a relatively smaller lean body mass.[16] The prevalence of hypomagnesemia in our study (~2.0%) was lower than in a previous study (4.6%), but this study used a different definition of hypomagnesemia (<0.75 mmol/L).[17] Of note, the prevalence of hypernatremia was higher in our study (3.1% to 3.7 %) compared with a previous study in community subjects (0.72%), despite the same definition of hypernatremia.[13] This difference may be related to the fact that we focused on subjects aged 55 years or more who are known to have a loss of renal-concentrating ability.[18] A recent study also showed that insensible water loss through skin and respiration increases with age,[19] which would predispose to hypernatremia. We were unable to find previously reported data on the prevalence of hypokalemia or hyperkalemia in the general population; our data suggest that hypokalemia is more common than hyperkalemia, although our cutoff for hyperkalemia may have been relatively high.

The strength of this study is that it is one of the first to study the risk factors of several electrolyte disorders in such a large cohort. This strengthens the relevance of the identified associations, and, indeed, many of these associations can be explained physiologically. For example, hypokalemia is a well-known adverse effect of loop- and thiazide diuretics, which is thought to develop because of secondary aldosteronism and flow-mediated kaliuresis.[20,21] Likewise, hyponatremia is a common adverse effect of thiazide di-

Table 4 Electrolyte Disorders and Mortality Risk

Electrolyte disorder	Deaths (n)	Crude*	Adjusted†
Hyponatremia	271	1.24 (1.09-1.40)	1.17 (1.02-1.34)
Hypernatremia	96	0.93 (0.76-1.14)	0.94 (0.76-1.17)
Hypokalemia	80	0.99 (0.80-1.24)	0.94 (0.74-1.19)
Hyperkalemia	13	2.08 (1.21-3.60)	1.42 (0.71-2.86)
Hypomagnesemia	62	1.45 (1.12-1.86)	1.39 (1.06-1.81)

*Adjustment for sex and age.

†Adjustment for sex, age, BMI, estimated glomerular filtration rate, diabetes mellitus, previous heart failure, and previous myocardial infarction.

uretics and antiepileptic drugs, either because they stimulate vasopressin secretion centrally or because of a direct antidiuretic effect in the kidney.[22-25] Selective serotonin reuptake inhibitors are another important cause of drug-induced hyponatremia,[26] but few subjects used this drug in The Netherlands at the time of data collection. Hypomagnesemia is believed to be caused by thiazides because they indirectly inhibit one of the renal magnesium transport proteins.[27] The associations among diabetes mellitus, hyponatremia, and hypomagnesemia have been reported.[28,29] Although hyperglycemia can cause hyponatremia, serum glucose levels were too low to fully explain the degree of hyponatremia using a common formula.[30] This suggests that diabetes mellitus or related glucose-lowering drugs predispose to hyponatremia. Although glucose-lowering drugs have been implicated in hyponatremia,[31,32] we previously found that diabetes mellitus was associated with hyponatremia independently of these drugs.[28] The exact mechanism of this association remains unknown but may be related to an interaction between insulin and vasopressin, both of which act in the renal collecting duct.[33,34] Stomach emptying also may have been slower in diabetic persons, which may have caused the reabsorption of more hypotonic fluid and, in the presence of vasopressin, may predispose to hyponatremia.[35] Several possible explanations for hypomagnesemia in diabetes mellitus have been reported, including poor dietary intake, glomerular hyperfiltration, altered insulin metabolism, osmotic diuresis, and recurrent metabolic acidosis.[29] Of interest, hypokalemia was associated with hypertension independently of diuretic use. Two mechanisms may contribute, although this is speculative. First, some of these subjects may have had primary aldosteronism, which causes hypokalemic hypertension and is more common than previously thought.[36] Alternatively, the presence of hypokalemia may have been a reflection of a low total body potassium content. Several studies have demonstrated that potassium depletion is a risk factor for the development of hypertension.[37,38] A lower BMI also was associated with an increased risk of hypokalemia (**Table 3**). Although low dietary intake of potassium alone is unlikely to cause hypokalemia, it may contribute when an additional cause of hypokalemia is present. No associations between estimated glomerular filtration rate with any of the electrolyte disorders were identified; we explain this because relatively few participants of this cohort had a low estimated glomerular filtration rate.

Our study also identified a number of new associations. First, the association between potassium-sparing diuretics and hyponatremia has not been reported on such a large scale. Although hyponatremia has been reported when amiloride or spironolactone was combined with thiazide diuretics,[39,40] our multivariable analysis suggests that the association between hyponatremia and potassium-sparing diuretics is independent. The association can be explained physiologically, because these drugs inhibit sodium reabsorption in the renal collecting duct, causing salt wasting with secondary vasopressin release due to hypovolemia.[20] Also, the association between loop diuretics and hypernatremia has not been reported. Loop diuretics prevent the generation of a concentration gradient in the renal medulla and therefore cause renal salt and water loss.[20] If this water loss is replaced insufficiently, hypernatremia may ensue.

Perhaps the most intriguing finding was the association between hyponatremia and benzodiazepines (**Table 3**, **Figure**). Whether this is a direct or indirect relationship is unclear, and we can only speculate about the possible mechanism. There is 1 well-documented case of lorazepam-induced hyponatremia, in which the development of hyponatremia was attributed to the syndrome of inappropriate antidiuretic hormone secretion.[41] Benzodiazepines influence the neurotransmitter gamma-aminobutyric acid, which has been shown to interact with vasopressinergic neurons.[42] However, because no subsequent cases or series have appeared, alternative explanations should be considered. One alternative explanation could be that sleeping disorders, for which benzodiazepines are usually prescribed, are associated with hyponatremia. Sleep deprivation can reduce cortisol levels.[43] Because cortisol is a tonic inhibitor of vasopressin, reduced cortisol levels may increase vasopressin and therefore predispose to hyponatremia. Alternatively, subjects using benzodiazepines often have psychologic or psychiatric disorders. A common symptom in such disorders is psychogenic polydipsia,[44] which will increase the risk of hyponatremia if there also is a stimulus for water retention, for example, due to thiazides. A direct drug–drug interaction between benzodiazepines and thiazides also remains possible, because in the kidney the peripheral benzodiazepine receptor is located near the target of thiazide diuretics.[45]

Because the majority of the observed electrolyte disorders was mild (**Table 2**), an important question is what the clinical implications are of our findings. Although 2 of the electrolyte disorders were associated with mortality, this may not be causal. On the other hand, a number of recent studies suggest that even mild electrolyte disorders can have adverse outcomes in the long term. For example, by using this same cohort, we recently showed that subjects who had hyponatremia at baseline had a higher risk of both vertebral and nonvertebral fractures during follow-up.[1] Because this association was independent of falls or osteoporosis, we hypothesized that chronic hyponatremia may have a direct effect on bone quality, as also was suggested by other studies.[46,47] Another recent study also showed that hyponatremia carried a poor prognosis in elderly community subjects, because it independently predicted death and myocardial infarction.[4] Although the outcomes of hypernatremia have not been studied at the population level, studies in hospitalized patients have shown that mortality rates start increasing when serum sodium exceeds 145 mmol/L, independently of the underlying disease.[48] Although no general population data on the outcomes of hypokalemia or hyperkalemia are available, studies in specific populations suggest higher mortality rates.[6,7] Obviously, in the case of diuretics, the beneficial effects of these drugs should be weighed against the potential complications of the associated electrolyte disorders.

Study Limitations

A number of potential limitations should be discussed. First, a limitation of our study may be the cross-sectional nature of our analyses. However, because of the population-based character and large participation proportion, substantial selection bias is probably unlikely. Moreover, misclassification of risk factors or measurement errors was probably random, because data collection occurred independently of the research question. Second, the differences between included and excluded participants (see "Materials and Methods") suggest a slightly better health status of the former. If anything, this would have led to an underestimation of the observed effects. Third, for drug-induced electrolyte disorders, the time of intake and possible underreporting of the dose taken are important, but often difficult to capture. Finally, it is important to emphasize that arterial rather than venous electrolyte concentrations correlate best with physiologic effects,[49] but these are difficult to obtain in such large cohorts.

CONCLUSIONS

The current study reveals a high prevalence of mostly mild electrolyte disorders in community subjects. Regular monitoring of serum electrolytes, discontinuation of offending drugs, and correction to normal levels may prove beneficial. However, an interventional study (correction vs no correction) would be required to substantiate this recommendation. If so, this would imply that general practitioners should measure serum sodium, potassium, and magnesium at regular intervals in subjects with diabetes mellitus and hypertension and those using diuretics or benzodiazepines.

References

1. Hoorn EJ, Rivadeneira F, van Meurs JB, et al. Mild hyponatremia as a risk factor for fractures: The Rotterdam Study. *J Bone Miner Res*. 2011;26:1822-1828.
2. Hoorn EJ, Zietse R. Hyponatremia and mortality: how innocent is the bystander? *Clin J Am Soc Nephrol*. 2011;6:951-953.
3. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med*. 2006;119:71 e1-8.
4. Sajadieh A, Binici Z, Mouridsen MR, Nielsen OW, Hansen JF, Haugaard SB. Mild hyponatremia carries a poor prognosis in community subjects. *Am J Med*. 2009;122:679-686.
5. Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. *Arch Intern Med*. 2010;170:294-302.
6. Ahmed A, Zannad F, Love TE, et al. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. *Eur Heart J*. 2007;28:1334-1343.
7. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351:543-551.
8. Beck LH. The aging kidney. Defending a delicate balance of fluid and electrolytes. *Geriatrics*. 2000;55:26-28, 31-32.
9. Hofman A, van Duijn CM, Franco OH, et al. The Rotterdam Study: 2012 objectives and design update. *Eur J Epidemiol*. 2011;26:657-686.
10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461-470.
11. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. *J Hypertens*. 1999;17:151-183.
12. Mosterd A, Hoes AW, de Bruyne MC, et al. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *Eur Heart J*. 1999;20:447-455.
13. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta*. 2003;337:169-172.
14. Hawkins RC. Gender and age as risk factors for hypokalemia and hyperkalemia in a multiethnic Asian population. *Clin Chim Acta*. 2003;331:171-172.
15. Kleinfeld M, Borra S, Gavani S, Corcoran A. Hypokalemia: are elderly females more vulnerable? *J Natl Med Assoc*. 1993;85:861-864.
16. Flynn MA, Nolph GB, Baker AS, Martin WM, Krause G. Total body potassium in aging humans: a longitudinal study. *Am J Clin Nutr*. 1989;50:713-717.
17. Syedmoradi L, Ghasemi A, Zahediasl S, Azizi F. Prevalence of hypo- and hypermagnesemia in an Iranian urban population. *Ann Hum Biol*. 2011;38:150-155.
18. Tian Y, Serino R, Verbalis JG. Downregulation of renal vasopressin V2 receptor and aquaporin-2 expression parallels age-associated defects in urine concentration. *Am J Physiol Renal Physiol*. 2004;287: F797-F805.
19. Dmitrieva NI, Burg MB. Increased insensible water loss contributes to aging related dehydration. *PLoS One*. 2011;6:e20691.
20. Ellison DH, Hoorn EJ, Wilcox CS. Diuretics. In: Taal MW, Chertow GM, Marsen PA, Skorecki K, Yu SL, eds. *Brenner and Rector's The Kidney*. 9th ed. Philadelphia, PA: Elsevier; 2011.
21. Satlin LM, Carattino MD, Liu W, Kleyman TR. Regulation of cation transport in the distal nephron by mechanical forces. *Am J Physiol Renal Physiol*. 2006;291:F923-F931.
22. de Braganca AC, Moyses ZP, Magaldi AJ. Carbamazepine can induce kidney water absorption by increasing aquaporin 2 expression. *Nephrol Dial Transplant*. 2010;25:3840-3845.
23. Friedman E, Shadel M, Halkin H, Farfel Z. Thiazide-induced hyponatremia. Reproducibility by single dose rechallenge and an analysis of pathogenesis. *Ann Intern Med*. 1989;110:24-30.
24. Hamburger S, Koprivica B, Ellerbeck E, Covinsky JO. Thiazide-induced syndrome of inappropriate secretion of antidiuretic hormone. Time course of resolution. *JAMA*. 1981;246:1235-1236.
25. Moses AM, Miller M. Drug-induced dilutional hyponatremia. *N Engl J Med*. 1974;291:1234-1239.
26. Fabian TJ, Amico JA, Kroboth PD, et al. Paroxetine-induced hyponatremia in older adults: a 12-week prospective study. *Arch Intern Med*. 2004;164:327-332.
27. Nijenhuis T, Vallon V, van der Kemp AW, Loffing J, Hoenderop JG, Bindels RJ. Enhanced passive Ca2+ reabsorption and reduced Mg2+ channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. *J Clin Invest*. 2005;115:1651-1658.
28. Beukhof CM, Hoorn EJ, Lindemans J, Zietse R. Novel risk factors for hospital-acquired hyponatraemia: a matched case-control study. *Clin Endocrinol (Oxf)*. 2007;66:367-372.
29. Pham PC, Pham PM, Pham SV, Miller JM, Pham PT. Hypomagnesemia in patients with type 2 diabetes. *Clin J Am Soc Nephrol*. 2007;2:366-373.
30. Matz R. Hyponatremia: evaluating the correction factor for hyperglycemia. *Am J Med*. 2000;108:180-181.
31. Weissman PN, Shenkman L, Gregerman RI. Chlorpropamide hyponatremia: drug-induced inappropriate antidiuretic-hormone activity. *N Engl J Med*. 1971;284:65-71.
32. Lichtenberg L, Abraira C. Tolbutamide-associated hyponatremia. *JAMA*. 1978;240:2433-2434.
33. Davis FB, Davis PJ. Water metabolism in diabetes mellitus. *Am J Med*. 1981;70:210-214.
34. Bustamante M, Hasler U, Kotova O, et al. Insulin potentiates AVP-induced AQP2 expression in cultured renal collecting duct principal cells. *Am J Physiol Renal Physiol*. 2005;288:F334-F344.

35. Carlotti AP, St George-Hyslop C, Guerguerian AM, Bohn D, Kamel KS, Halperin M. Occult risk factor for the development of cerebral edema in children with diabetic ketoacidosis: possible role for stomach emptying. *Pediatr Diabetes*. 2009;10:522-533.
36. Kaplan NM. The current epidemic of primary aldosteronism: causes and consequences. *J Hypertens*. 2004;22:863-869.
37. Krishna GG, Kapoor SC. Potassium depletion exacerbates essential hypertension. *Ann Intern Med*. 1991;115:77-83.
38. Krishna GG, Miller E, Kapoor S. Increased blood pressure during potassium depletion in normotensive men. *N Engl J Med*. 1989;320: 1177-1182.
39. Handler J. Well tolerated spironolactone-related hyponatremia. *J Clin Hypertens (Greenwich)*. 2008;10:317-321.
40. Strykers PH, Stern RS, Morse BM. Hyponatremia induced by a combination of amiloride and hydrochlorothiazide. *JAMA*. 1984;252:389.
41. Engel WR, Grau A. Inappropriate secretion of antidiuretic hormone associated with lorazepam. *BMJ*. 1988;297:858.
42. Yamaguchi K, Hama H. Changes in vasopressin release and autonomic function induced by manipulating forebrain GABAergic signaling under euvolemia and hypovolemia in conscious rats. *Endocr J*. 2011; 58:559-573.
43. Vgontzas AN, Mastorakos G, Bixler EO, Kales A, Gold PW, Chrousos GP. Sleep deprivation effects on the activity of the hypothalamic-pituitary-adrenal and growth axes: potential clinical implications. *Clin Endocrinol (Oxf)*. 1999;51:205-215.
44. Illowsky BP, Kirch DG. Polydipsia and hyponatremia in psychiatric patients. *Am J Psychiatry*. 1988;145:675-683.
45. Lukeman DS, Fanestil DD. Interactions of diuretics with the peripheral-type benzodiazepine receptor in rat kidney. *J Pharmacol Exp Ther*. 1987;241:950-955.
46. Barsony J, Sugimura Y, Verbalis JG. Osteoclast response to low extracellular sodium and the mechanism of hyponatremia-induced bone loss. *J Biol Chem*. 2011;286:10864-10875.
47. Verbalis JG, Barsony J, Sugimura Y, et al. Hyponatremia-induced osteoporosis. *J Bone Miner Res*. 2010;25:554-563.
48. Funk GC, Lindner G, Druml W, et al. Incidence and prognosis of dysnatremias present on ICU admission. *Intensive Care Med*. 2010; 36:304-311.
49. Shafiee MA, Charest AF, Cheema-Dhadli S, et al. Defining conditions that lead to the retention of water: the importance of the arterial sodium concentration. *Kidney Int*. 2005;67:613-621.