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ORIGINAL RESEARCH

Impact of Female Sex on the Susceptibility to Hypernatremia Among Older Community-Dwelling Individuals in Japan

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Purpose: Older individuals are at high risk for hypernatremia. However, actual data on serum sodium levels and differences between the sexes remain unclear in the older Japanese population. This study aimed to describe the data regarding serum sodium level and hypernatremia prevalence and to investigate whether female sex is associated with an increased risk of hypernatremia.

Patients and Methods: We retrospectively analyzed the data of adults aged ≥65 years without severely reduced kidney function who underwent an annual health checkup in 2019. Serum sodium levels were investigated as the outcome and corrected for glucose, if necessary. Clinical characteristics were compared between women and men.

Results: In the 903 participants consisting of 273 women and 630 men who were enrolled in this study, the overall prevalence of hypernatremia, defined as a serum sodium level ≥145 mmol/L, was 12.5%. Female participants showed significantly more frequent hypernatremia than male participants (17.6% vs 10.3%, p = 0.003) and higher serum sodium levels (median [interquartile range]; 143.0 [142.0, 144.0] vs 142.4 [141.5, 144.0], p <0.001). Serum creatinine (sCr), but not estimated glomerular filtration rate (eGFR), was correlated with serum sodium levels (r_s = −0.108, p = 0.001). In the binary logistic regression analysis, female sex was significantly associated with hypernatremia (odds ratio, 1.89; 95% confidence interval, 1.23–2.89; p = 0.004) even after adjusting for age, alcohol use, antihypertensive agent use, body mass index, and winter season. The association between female sex was reduced and no longer significant after adjusting for sCr, although the association remained unchanged after adjustment for eGFR.

Conclusion: One-eighth of the older community dwellers in Japan exhibits hypernatremia after an overnight fast, and female sex is a significant risk factor. Since sCr is a surrogate of muscle mass, smaller muscle mass possibly mediates the association between female sex and hypernatremia.

Keywords: elderly, sex, sodium, water, community dwellers

Introduction

Dysnatremia is a common clinical problem in older individuals. The serum sodium concentration is determined by the net sodium content and total body water, and absolute or relative deficiency of free water is the major cause of hypernatremia.[1] Older individuals are at high risk of hypernatremia because of their decreased total body water content, blunted thirst sensation, and decreased urinary concentrating ability.[2] Since even mild hypernatremia, such as serum sodium level of ≥145 mmol/L, is significantly associated with cardiovascular disease events and deaths in older community dwellers, hypernatremia in older persons is a crucial problem in Japan, considering the rapidly increasing aging population.[3]

In Japan, although the prevalence of hypernatremia in older individuals has been investigated in the emergency department setting, the prevalence of hypernatremia among the older community dwellers in Japan remains unknown.[4]

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Previously, we found that most community-dwelling older individuals had a plasma osmolality of ≥300 mOsm/L in the early morning after an overnight fast, suggesting water-loss dehydration.[5] Therefore, we presumed that hypernatremia among community-dwelling older individuals in Japan may be overlooked.

The first objective of this study was to analyze the data regarding the serum sodium levels and describe the prevalence of hypernatremia in this population. Additionally, we hypothesized that older women are more prone to hypernatremia than men because women have less muscle mass, the main reservoir of body water, and carry a smaller amount of body water than men.[6,7] Thus, the second objective of this study was to investigate whether female sex is associated with an increased risk of hypernatremia.

Patients and Methods

Study Setting and Participants

This was a single-center, retrospective, cross-sectional study. Participants' selection was performed as in our previous work.[5] Community-dwelling adults who had undergone an annual health checkup at Nihon University Hospital (Tokyo, Japan) between January 2019 and December 2019 were potentially eligible. The exclusion criteria were as follows: (1) aged <65 years, (2) unmeasured serum sodium level, and (3) severely reduced kidney function: estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2.

Studied Parameters

Blood and urine samples were collected early in the morning after an overnight fast. Participants were instructed to finish dinner by 9:00 pm the night prior to the health checkup, while they could drink water until bedtime. After waking, ≤200 mL water consumption was allowed if they were thirsty.

Age, sex, height, weight, and blood pressure were recorded as background characteristics. Blood pressure in the sitting position was measured twice using the oscillometric method, and the average value was used. Body mass index (BMI) was determined by dividing body weight by height squared. Information about habitual alcohol consumption, medical history, and presence or absence of medication for hypertension and diabetes mellitus (DM) was collected using a self-reported questionnaire. This was designed for a specific health checkup program according to the guidance of the Ministry of Health, Labor and Welfare in Japan (https://www.mhlw.go.jp). It was also noted whether the health checkup was performed during the winter season (December, January, and February), because a previous study had reported a higher prevalence of hypernatremia during the winter season in older Japanese persons in the emergency department setting.[4]

The laboratory parameters studied included serum sodium, serum creatinine (sCr), plasma glucose, glycated hemoglobin (HbA1c) and urine-specific gravity (USG). Since hyperglycemia can modify the serum sodium levels, we corrected serum sodium levels for glucose in participants with plasma glucose of >100 mg/dL, using the following equation: $\text{Measured serum sodium}[\text{mmol/L}] + 1.6 \times (\text{Plasma glucose}[\text{mg/dL}] - 100)/100$.[8] Finally, participants who showed a serum sodium level of ≥145 mmol/L were judged to have hypernatremia. Blood urea nitrogen (BUN) was also studied to determine the blood urea nitrogen-to-creatinine ratio (BCR). The eGFR was calculated using the following formula: $194 \times \text{sCr}[\text{mg/dL}]^{-1.094} \times \text{Age}[\text{years}]^{-0.287} (\times 0.739 \text{ if female})$.[9]

Participants were considered to have hypertension if any of the following is applied: self-reported history of hypertension, medication for hypertension, systolic BP ≥140 mmHg, or diastolic BP ≥90 mmHg. Participants were considered to have DM if any of the following applied: self-reported history of DM, medication for DM, fasting glucose ≥126 mg/dL, or HbA1c ≥6.5%. Participants with eGFR <60 mL/min/1.73 m^2 were considered to have chronic kidney disease (CKD).

Statistical Analysis

We divided the enrolled participants according to sex and compared the data between women and men. Continuous variables are presented as mean ± standard deviation or median [interquartile range], as appropriate. For comparisons between the two groups, differences in continuous variables were examined using Student's *t*-test or Mann–Whitney *U*-test. Differences in the percentage data were examined using the Chi-square test.

While the sCr provides eGFR value for assessment of kidney function, the sCr level itself is well correlated with muscle mass.[9–12] Spearman's rank correlation coefficient was used to determine the associations between sCr and serum sodium level, and that between the eGFR and serum sodium levels.

Binary logistic regression analysis was performed to investigate the impact of the variables on the presence of hypernatremia. Multivariate logistic regression analysis using the forced entry method was performed to identify whether female sex was independently associated with hypernatremia after adjusting for other variables. Hypernatremia was used as the dependent variable. Female sex (1, yes; 0, no), age (per year), habitual alcohol consumption (1, yes; 0, no), antihypertensive agent use (1, yes; 0, no), BMI (per kg/m^2), and checkup during the winter season (1, yes; 0, no) were included into the multivariate model (model 1). To assess the potential mediating effect of muscle mass on the relationship between female sex and serum sodium level, the multivariate model 1 was further adjusted for sCr (mg/dL) (model 2). Similarly, model 1 was adjusted for eGFR (mL/min) to evaluate the effect of kidney function (model 3).

For all statistical analyses, we used EZR version 1.50 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 3.63 (The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.01$.

Results

Background Characteristics of Studied Participants

Figure 1 summarizes the participants' selection procedure. Overall, 11,633 participants, consisting of 4794 women and 6839 men, were potentially eligible, but 10,730 participants were excluded based on the criteria, largely due to their age, and 903 participants were finally enrolled in this study. Our cohort had a female-to-male ratio of 3:7; the median age was 68 [66, 71] years (Table 1).

Comparison Between Female and Male Participants

Overall, the prevalence of hypernatremia was 12.5% (113 of total 903 participants). Figure 2 indicates the distribution of serum sodium. The serum sodium levels of female participants were distributed at a higher level relative to those of males regardless of correction for glucose. Table 2 shows the comparison of the characteristics between female and male participants. The serum sodium levels were significantly higher, and hypernatremia was more frequently prevalent in female participants (17.6% vs 10.3%, $p = 0.003$). Female participants showed lower BMI values and less frequent DM than did male participants. Accordingly, fasting plasma glucose level was significantly lower in females. However, the serum sodium levels remained higher in female participants even after sodium correction for glucose. Although the sCr was significantly lower in females, the eGFR value and prevalence of CKD did not differ. BCR levels were significantly higher in females than in males. Meanwhile, female participants had significantly lower USG level than males, despite their higher levels of serum sodium and BCR.

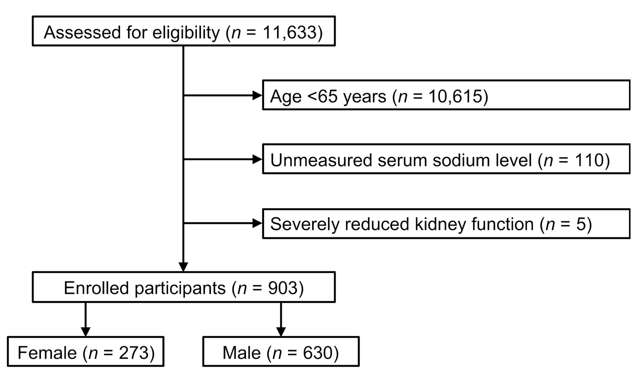

Figure 1 Participant selection procedure.
Abbreviation: eGFR, estimated glomerular filtration rate.

Table 1 Background Characteristics of Study Participants

Variables	Values (n = 903)
Female (n, %)	273 (30.2)
Age (years)	68 [66, 71]
Body mass index (kg/m^2)	23.3 ± 3.3
Habitual alcohol use (n, %)	235 (26.2)
Hypertension (n, %)	256 (28.4)
Antihypertensive agent use (n, %)	155 (17.2)
Diabetes mellitus (n, %)	209 (23.2)
Anti-diabetic agent use (n, %)	54 (6.0)

Note: Data are presented as the mean ± standard deviation, the median [interquartile range], or as a number with a percentage.

Correlation Analyses Between sCr, eGFR and Serum Sodium Level

Correlations between sCr, eGFR and serum sodium level were evaluated, respectively. The relationships are illustrated in Figure 3. The sCr level was significantly inversely correlated with serum sodium level ($r_s = -0.108$, $p = 0.001$), although the correlation was weak. Meanwhile, no significant correlation was found between the eGFR and serum sodium levels.

Factors Associated with Hypernatremia Evaluated Using Binary Logistic Regression Analysis

Table 3 shows the results of the binary logistic regression analysis using hypernatremia as the dependent variable. Female sex was significantly associated with an increased risk of hypernatremia even after adjusting for the effects of age, alcohol use, antihypertensive agent use, BMI, and winter season (adjusted odds ratio [OR], 1.89; 95% confidence interval [CI], 1.23–2.89; $p = 0.004$). Adjustment for eGFR did not alter the association between female sex and hypernatremia (adjusted OR, 1.89; 95% CI, 1.23–2.89; $p = 0.004$). However, the effect of female sex on hypernatremia was reduced, and the association was no longer significant after adjusting for sCr (adjusted OR, 1.68; 95% CI, 0.99–2.86; $p = 0.053$).

Discussion

This study demonstrated that the prevalence rate of hypernatremia after an overnight fast was 12.5% overall, 17.6% in females, and 10.3% in males for community-dwelling older individuals in Japan. Female participants showed significantly higher serum sodium levels, and female sex was associated with an increased risk of hypernatremia even after

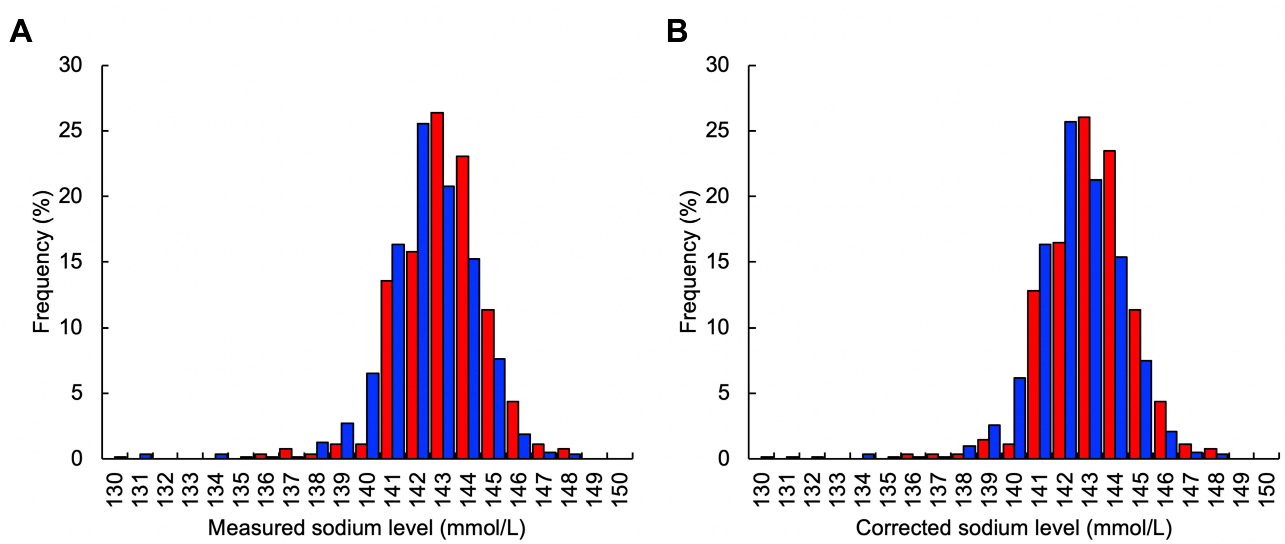

Figure 2 Distribution of participants by serum sodium level with respect to sex. (**A**) Distribution based on measured sodium level. (**B**) Distribution after sodium correction for glucose. The horizontal axis indicates serum sodium level (mmol/L). The vertical axis indicates the frequency (%). Red bars, female; Blue bars, male.

Table 2 Comparison Between Females and Male Participants

Variables	Female (n = 273)	Male (n = 630)	*p*
Measured Sodium (mmol/L)	143 [142, 144]	142 [141, 144]	<0.001
Corrected sodium (mmol/L)	143.0 [142.0, 144.0]	142.4 [141.5, 144.0]	<0.001
Hypernatremia (n, %)	48 (17.6)	65 (10.3)	0.003
Age (years)	68 [66, 72]	68 [66, 71]	0.81
Body mass index (kg/m^2)	21.8 ± 3.3	23.9 ± 3.1	<0.001
Habitual alcohol use (n, %)	69 (25.3)	166 (26.3)	0.8
Hypertension (n, %)	64 (23.4)	192 (30.5)	0.038
Antihypertensive agent use (n, %)	36 (13.2)	119 (18.9)	0.047
Systolic blood pressure (mmHg)	119.6 ± 15.5	120.3 ± 13.5	0.52
Diastolic blood pressure (mmHg)	76.2 ± 11.3	77.4 ± 11.0	0.13
Diabetes mellitus (n, %)	42 (15.4)	167 (26.5)	<0.001
Anti-diabetic agent use (n, %)	13 (4.8)	41 (6.5)	0.39
Creatinine (mg/dL)	0.66 [0.60, 0.74]	0.88 [0.80, 1.00]	<0.001
eGFR (mL/min/1.73 m^2)	67.2 ± 11.5	65.9 ± 11.9	0.13
BCR	21.9 [19.5, 26.1]	17.6 [15.1, 20.4]	<0.001
Chronic kidney disease (n, %)	72 (26.4)	199 (31.6)	0.14
Plasma glucose (mg/dL)	98.0 [92.0, 104.0]	104.0 [97.0, 116.8]	<0.001
Glycated hemoglobin (%)	5.9 [5.7, 6.2]	5.9 [5.7, 6.3]	0.066
Urine specific gravity	1.012 [1.009, 1.018]	1.017 [1.012, 1.021]	<0.001

Note: Data are presented as the mean ± standard deviation, the median [interquartile range], or as a number with a percentage.
Abbreviations: BCR, blood urea nitrogen-to-creatinine ratio; eGFR, estimated glomerular filtration rate.

adjusting for the effects of age, alcohol use, antihypertensive agent use, BMI, and winter season. sCr showed an inverse correlation with serum sodium levels, and the adjustment for sCr attenuated the association between female sex and hypernatremia.

In this study, we found that female sex was associated with a risk of hypernatremia in older community dwellers in Japan. Although sudden and very large sodium supplementation can raise the serum sodium level, hypernatremia development fundamentally requires water deficiency.[1,13] Since this study investigated an annual health checkup data in community dwellers, it is thought that hypernatremia reflects water-loss dehydration rather than a large amount of sodium supplementation. It should be also noted that women showed higher BCR than men in our present study. BUN is a byproduct of protein metabolism that is filtered out of the blood by the kidney. Since increased sodium and water

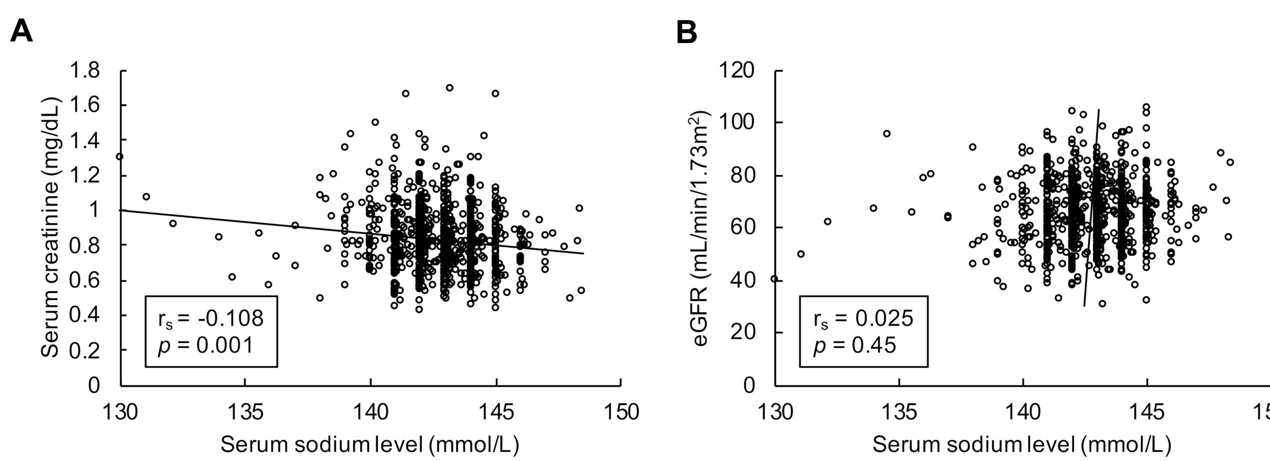

Figure 3 Associations between serum creatinine (sCr), estimated glomerular filtration rate (eGFR) and serum sodium level. The horizontal axis indicates serum sodium level. Correlation analyses were validated using Spearman's rank correlation coefficient. (**A**) sCr showed weak but significant inverse correlation with serum sodium level (r_s = −0.108, p = 0.001). (**B**) There was no significant correlation between eGFR and serum sodium level (r_s = 0.025, p = 0.45).

Table 3 Binary Logistic Regression Analysis Using Hypernatremia as the Dependent Variable

	Model 1		Model 2 (with adjustment for sCr)		Model 3 (with adjustment for eGFR)	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Female sex	1.89 (1.23–2.89)	0.004	1.68 (0.99–2.86)	0.053	1.89 (1.23–2.89)	0.004
Age	1.01 (0.97–1.06)	0.59	1.01 (0.97–1.06)	0.53	1.01 (0.97–1.06)	0.52
Winter season	0.99 (0.61–1.61)	0.98	0.99 (0.61–1.61)	0.97	0.99 (0.61–1.60)	0.96
Habitual alcohol use	1.03 (0.65–1.61)	0.91	1.03 (0.65–1.62)	0.91	1.03 (0.65–1.62)	0.90
Antihypertensive agent	1.10 (0.65–1.86)	0.72	1.10 (0.65–1.87)	0.72	1.10 (0.65–1.86)	0.72
Body mass index	1.01 (0.95–1.07)	0.86	1.01 (0.95–1.07)	0.77	1.01 (0.95–1.07)	0.78

Notes: Female sex (1, yes; 0, no), age (per year), checkup during the winter season (1, yes; 0, no), habitual alcohol use (1, yes; 0, no), antihypertensive agent use (1, yes; 0, no), and body mass index (per kg/m^2) were included into multivariate model 1. Model 2, model 1 + adjustment for sCr (mg/dL); Model 3, model 1 + adjustment for eGFR ($mL/min/1.73m^2$).

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; sCr, serum creatinine.

reabsorption during dehydration is accompanied by an increase in BUN reabsorption, the higher BCR in women is consistent with a higher prevalence of hypernatremia due to water deficiency.

Previous studies have shown mixed results regarding the sex difference in hypernatremia and water-loss dehydration. In a retrospective study that reviewed patients aged ≥60 years who were admitted to a community teaching hospital in America, hypernatremia confirmed at admission was significantly associated with female sex, greater age, and nursing home residence.[14] In contrast, a study based on the National Health and Nutrition Examination Survey data showed that hypertonicity (plasma tonicity ≥300 mmol/L) was associated with male sex, older age, and DM.[15] That study also reported that African-Americans and Mexican-Americans showed hypertonicity more frequently than non-Hispanic Whites. Another study based on the Medicare Provider Analysis and Review showed that hospitalization with a diagnosis of dehydration in Americans aged ≥65 years occurred more frequently in men than in women, and in African-Americans more than in non-Hispanic Whites.[16] In Japan, a previous study conducted in nursing homes reported that the proportion of females judged to be dehydrated or not was 80.0% and 83.8%, respectively, and the difference was not significant.[17] Since diverse factors, such as age, sex, race, and environment can influence the ability of fluid reservation, the results may depend on the study setting. Our present study suggests that older Japanese community-dwelling women are more predisposed to hypernatremia than men.

Since our present study was based on health checkup data, none of the enrolled patients showed severe hypernatremia. However, previous studies have shown a substantial clinical impact from mild hypernatremia in community-dwelling older individuals. A prospective cohort study in England found that older male individuals who had serum sodium levels exceeding 143 mmol/L showed significantly higher incidence rates of coronary vascular disease events and all-cause deaths during an 11-year follow-up period compared with those who had sodium levels of 139–143 mmol/L.[3] A study based on the National Health and Nutrition Examination Survey reported that older community dwellers with a higher serum sodium level (mean 145.4 mmol/L, median 145.0 mmol/L) have a significantly lower survival rate relative to those with a normal sodium level (136–144 mmol/L).[18] Additionally, it was reported that community-dwelling older men with a higher serum sodium level (144 ± 1 mmol/L) had an increased risk of cognitive decline when compared with a reference group (142 ± 2 mmol/L).[19] In Japan, the odds of reduced maximum voluntary tongue pressure against the plate, which relates to dysphagia and dysphasia, was reported to be approximately twice as high in older community-dwelling men with a serum sodium level of 143–145 mmol/L than those with a serum sodium level of 135–140 mmol/L, even after adjusting for confounding factors.[20] Mild hypernatremia and its clinical impacts should not be overlooked. Our present study confirmed that one-sixth of the female and one-tenth of the male community-dwelling older persons in Japan had serum sodium levels ≥145 mmol/L.

Based on previous reports, there are possible explanations for the susceptibility of females to hypernatremia. First is the sex difference in urine concentrating ability. Increased serum sodium levels increase plasma osmolarity, which is sensed by osmoreceptors on the hypothalamus, which in turn stimulates thirst and antidiuretic hormone (ADH) secretion. ADH strongly promotes water reabsorption in the renal collecting duct to concentrate urine. This response is the main determinant of water excretion. Intriguingly, the response of ADH secretion to increased plasma osmolality was reported to be more sensitive in men than in women.[21] Additionally, it was reported that women excrete less concentrated urine than men, even after adjusting for age, weight, serum creatinine level, and dietary nutrients.[22] In this present study, intriguingly, female participants showed significantly lower USG than males despite their higher serum sodium levels. The results indicate that a blunted response of urine concentration to hypernatremia is associated with the sex difference of hypernatremia susceptibility.

A second possible explanation pertains to the relatively small muscle mass in women compared with that in men. Water is the major component of the human body and is mainly distributed in the lean mass; thus, the muscles are thought to be the main reservoir of body water.[6] Testosterone enhances muscle protein synthesis and increases muscle mass.[23] Therefore, in comparison with males, females gain less lean mass during puberty and have less muscle mass in adulthood.[24–26] Creatinine is produced nonenzymatically and irreversibly from muscle creatine at a constant daily rate and filtered out of the blood by the renal glomeruli with minimal tubular reabsorption.[27] Therefore, it can serve as a chemical marker of kidney function and the amount of muscle mass in a steady state. Significant differences in sCr levels between male and female groups were observed in this present study. However, the eGFR and the coexistence of CKD did not differ between the two sexes, indicating that lower sCr in female group reflects a smaller amount of muscle mass. We found that the sCr level was inversely correlated with serum sodium level, and adjustment for sCr attenuate the relationship between female sex and hypernatremia risk in binary logistic regression analysis, although adjustment for eGFR did not alter the association. These results suggest that smaller muscle mass partially explains the susceptibility of females to water deficiency, leading to the hypernatremia.

The effects of steroid hormones are also a considerable issue when discussing water and salt regulation. Aldosterone primarily regulates renal sodium reabsorption. Meanwhile, it was reported that excess aldosterone could induce upward resetting of the osmostat and lead to mild hypernatremia in cases of primary aldosteronism.[28] In young adults, there is a sex difference in the level of aldosterone. Since progesterone increases aldosterone production, the aldosterone level is increased during the luteal phase in premenopausal women.[21,29] Because of this menstrual fluctuation, premenopausal women have a higher aldosterone level during the luteal phase compared with that in men.[21] However, the sex difference of plasma aldosterone level was not seen after menopause.[30] Since our present cohort investigated participants aged ≥65 years, the sex difference of these steroids was less likely to have contributed to the association between female sex and hypernatremia observed in this study.

It should be also noted that women showed lower plasma glucose levels than men in our present study. From a physiological point of view, increased glucose levels lead to increased osmolality, which releases water out of the cells into the extracellular space, thereby lowering the serum sodium concentration. Since the sex difference in glucose level could potentially affect the results, we adopted the serum sodium correction for glucose proposed by Katz in this study.[8] However, as shown in Figure 2, the correction altered the results of sodium levels in a few patients, but the influence seems trivial in a broad perspective. While the association between high glucose and hypernatremia risk should be evaluated in populations with DM, our study results indicate glucose level only marginally mediates the association between female sex and hypernatremia in general older population in Japan.

There are some limitations to the present study. First, this study was based on data from an annual health checkup consisting of general laboratory tests and self-reported questionnaires. Therefore, information about detailed medical history, physical examination for dehydration, adherence to overnight fast procedure, ordinary intake, and urinary excretion of water and sodium were unavailable. Since these parameters exert important roles in assessing sodium and water balance, the underlying etiology of hypernatremia in women remains unknown in this study. Second, classes of antihypertensive agents were unavailable in this study. While diuretics and renin-angiotensin-aldosterone blockades are well-known agents causing water and electrolyte imbalances in older individuals, a self-report questionnaire for a specific health checkup program was not designed to collect drug names of antihypertensive agents (https://www.mhlw.go.jp).[31,32] These unmeasured confounding factors may have affected the study results. Third, while sCr is well correlated with lean mass, the gold standard for muscle mass measurement is dual-energy X-ray absorptiometry. The mediating effect of muscle mass on the association between female sex and serum sodium level should be validated using dual-energy X-ray absorptiometry in future studies. Lastly, participants who had undergone an annual health checkup at our hospital tended to be male both overall and in the older population, indicating a referral bias may exist. Further prospective studies are required to validate the mechanism and generalizability of susceptibility to hypernatremia due to female sex.

Conclusion

One-eighth of community-dwelling older individuals in Japan exhibited hypernatremia, defined as serum sodium level ≥145 mmol/L after an overnight fast. The prevalence rate of hypernatremia was significantly higher among women than among men, and female sex was significantly associated with an increased risk of hypernatremia. It should be noted that one-sixth of older women have hypernatremia after an overnight fast. The mediating effect of smaller muscle mass on the association between female sex and hypernatremia was suggested, and further research is required to determine the underlying etiology of females' susceptibility to hypernatremia.

Abbreviations

ADH, anti-diuretic hormone; BCR, blood urea nitrogen-to-creatinine ratio; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1C, glycated hemoglobin; sCr, serum creatinine; USG, urine-specific gravity.

Ethics Approval and Informed Consent

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Nihon University Hospital (No. 20200301, approved on March 14, 2020). The requirement for written informed consent was waived because this was a retrospective observational study, and an opt-out recruitment procedure was followed.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest regarding the contents of this article.

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