Mild Hyponatremia is Associated with Low Skeletal Muscle Mass, Physical Function Impairment, and Depressive Mood in the Elderly

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Abstract

Background: Mild hyponatremia (serum sodium 130-135 mEq/L) is a common electrolyte disorder in the elderly. However, its association with both sarcopenia and cognitive function remains to be clarified. Therefore, here we investigated the association of mild hyponatremia with skeletal muscle mass, physical function, and cognitive function in the elderly.

Methods: We enrolled 75 participants with mild hyponatremia and 2872 with normonatremia (serum sodium, 136-145 mEq/L) aged ≥70 years who visited the Memory Disorder Outpatient Center of Japan's National Center for Geriatrics and Gerontology. Skeletal muscle mass index (SMI), grip strength (GS), walking speed (WS), one-leg standing (OLS) test times, and neuropsychological test scores were determined.

Results: One-way analysis of covariance showed that the participants with mild hyponatremia had significantly lower SMI, GS, WS, OLS time, and score on the 15-item Geriatric Depression Scale compared with those with normonatremia. Multiple logistic regression analysis indicated that mild hyponatremia was independently associated with weaker GS (odds ratio [OR]: 2.3, p = 0.048), slower WS (OR: 7.6, p = 0.01) and shorter OLS time (OR: 2.1, p = 0.03) as well as with severe depressive mood (OR: 2.6, p = 0.001) but not with sarcopenia (OR: 1.9, p = 0.09) or SMI (OR: 1.7, p= 0.1).

Conclusions: Our results suggest mild hyponatremia in the elderly was associated with impairment of physical function, especially including WS and OLS, and depressive mood.

Background

Hyponatremia is the most common electrolyte disorder in the elderly. It occurs in about 7% of all otherwise healthy people aged 55 years or more, with incidence increasing significantly with age.(1) The most common clinical etiologies of hyponatremia in the elderly are medication use (especially of diuretics and antidepressants), syndrome of inappropriate antidiuretic hormone secretion, malnutrition, and endocrinopathy.[1] In most cases though, the symptoms of hyponatremia are mild and related symptoms are subtle, so it often goes unnoticed by patients and physicians.

However, recent studies suggest that asymptomatic hyponatremia is associated with poor prognosis in the elderly. Largely asymptomatic mild-to-moderate hyponatremia was reported to be associated with gait instability, falls, and fractures.(2–4) Also, even after considering the many etiologies of hyponatremia that may contribute to poor prognosis among the elderly, hyponatremia itself is considered to be an independent risk factor for poor prognosis.(2) Attention deficit has also been reported in both humans and rats with mild-to-moderate hyponatremia.(3, 5) Thus, it seems plausible that asymptomatic hyponatremia contributes to poor prognosis through, for example, falls or fractures probably as a result of impaired attention, posture, and gait.

To date, most studies on the association between physical function and hyponatremia have involved patients with moderate hyponatremia (serum sodium [SNa] < 130 mEq/L).(3) So, it remains unclear whether there is an association between mild hyponatremia (SNa 130–135 mEq/L), which constitutes most cases of hyponatremia, and both physical and cognitive function in the elderly. In clinical practice, physicians are often hesitant to treat asymptomatic mild hyponatremia with SNa ≥ 130 mEq/L. However, increased mortality has been reported in patients hospitalized with even mild hyponatremia (SNa 130–134 mEq/L).(6) Thus, we hypothesized that elderly people with even mild hyponatremia, not just those with mild-to-moderate hyponatremia, have physical or cognitive dysfunction such as impaired balance or executive dysfunction. We also hypothesized that there is an the association between mild hyponatremia and lower skeletal muscle mass (SMM) in this population based on a report that found an association between chronic hyponatremia and decreased SMM in rats.(7)

Because homeostatic responses to environmental challenges decline with aging, hyponatremia is frequently diagnosed in the elderly. We anticipate that more frail elderly patients will present with mild hyponatremia into the future society ages. So, if mild hyponatremia is associated with physical or cognitive dysfunction, then we should consider ways to prevent and manage this condition.

In this study, we investigated the association between mild hyponatremia and SMM, physical function, and neuropsychological test scores.

Methods

Participants

We enrolled 2872 elderly participants with normonatremia (SNa 136–145 mEq/) and 75 with mild hyponatremia (SNa 130–135 mEq/L) aged ≥ 70 years who visited the National Center for Geriatrics and Gerontology (NCGG) for assessment of memory disorder between September 2010 and November 2017. None of the participants had any severe symptoms such as nausea, vomiting, confusion, or seizures, and all were able to carry out at least 1 of the following 3 physical function tests: grip strength (GS), walking speed (WS), and the one-leg standing (OLS) test. To eliminate pseudohyponatremia and the effect of disease on physical or cognitive function, the following inclusion criteria were adopted: (1) no history of stroke; (2) no anemia (hemoglobin ≥ 11.0 g/dL); (3) no acute illness (C-reactive protein < 1); (4) no severe renal dysfunction (estimated glomerular filtration rate > 15 mL/min/1.73 m^2); (5) no thyroid dysfunction (thyroid stimulating hormone ≤ 10 μIU/ml; (6) serum osmolality < 300 mOsm/kg; and (7) potassium ≥ 3.5 mEq/L.

The study was approved by the NCGG Ethics Committee. All participants provided informed consent before enrollment in the study.

Clinical Measures

The following self-reported and caregiver-reported measures were obtained: age, sex, and years of education, Barthel Index (BI) score, alcohol consumption, history of heart disease, diabetes, liver disease, cancer, joint pain, visual impairment, hearing impairment, and frequency of physical activity. Those who consumed > 60.0 g/day of alcohol were defined as heavy drinkers. No exercise per week was defined as inactivity. Use of diuretics and central nervous system (CNS) active drugs were checked by neuropsychologists from prescription records. CNS active drugs included antiepileptic, antipsychotic, antidepression, and benzodiazepine drugs. Systolic blood pressure was measured using an automatic blood pressure monitor at the time of physical function assessment. Hypotension was defined as blood pressure < 100 mmHg. Patients were excluded is their blood work was positive for brain natriuretic peptide, C-reactive protein, hemoglobin, thyroid stimulating hormone, or potassium.

Assessment of SMM, physical function, and sarcopenia

Body weight (BW) and SMM were assessed using a multi-frequency body composition analyzer (MC-180 Multi-Frequency Body Composition Analyzer; Tanita, Tokyo, Japan), which is a scale that uses bioelectrical impedance analysis to determine body composition. We calculated body mass index (BMI) (body weight in kg/height in m^2) and skeletal muscle mass index (SMI; SMM in kg/height m^2). Low SMM was defined as SMI < 7.0 kg/m^2 in men and < 5.7 kg/m^2 in women.(8)

Physical function was assessed by measuring GS, WS, and OLS time, Muscle strength was from upper extremity strength measured with a digital force gauge (ZP 500N; Imada, Toyohashi, Japan).(9) The average GS (kg) on both sides was determined, with low muscle strength defined as < 28 kg in men and < 18 kg in women, in accordance with the Asian Working Group for Sarcopenia (AWGS) criteria.(8) Velocity was determined by measuring normal WS, with poor physical performance defined as WS < 1.0 m/s.(8) Postural function was assessed with the OLS test, which measures the time in seconds (up to a maximum of 60 s) that participants can stand unassisted on one leg for as long as possible with their eyes open. Both legs were tested, and the average was used for analysis.(10) Impaired postural function was defined as OLS time ≤ 5 s.(11) Sarcopenia was defined as low SMM, low muscle strength, and/or low physical function.(8)

Assessment of cognitive function

Cognitive function was assessed using the Mini–Mental State Examination (MMSE),(12) executive function with the Frontal Assessment Battery (FAB),(13) working memory with the Digit Span subtest (forward and backward) of the Wechsler Adult Intelligence Scale,(14) attention with the category fluency subtest of the Hasegawa Dementia Rating Scale-Revised,(15) and memory with the Logical Memory II subtest of the Wechsler Memory Scale-Revised (WMS-R).(16)

Cognitive impairment was indicated by MMSE score ≤ 23, FAB score ≤ 11,(17) Digit Span forward score ≤ 5, Digit Span backward score ≤ 3, category fluency test score ≤ 5, and WMS-R Logical Memory II subtest raw score≤ 8 for > 16 years of education, ≤ 4 for 8–15 years of education and ≤ 2 for 0–7 years

of education.(18) Depressive mood was assessed using the GDS-15,(19) with a score ≥ 10 indicating severe depressive mood.(20) All of the cognitive test results were reviewed by neuropsychologists.

Statistical analysis

The Chi-squared test and Mann–Whitney's U test were used to investigate differences in characteristics between the 2 groups. One-way analysis of covariance (ANCOVA) was used to identify significant differences between the 2 groups in SMI, the 3 physical function test scores, and all the neuropsychological test scores after controlling for covariates. Then, multiple logistic regression analysis was conducted to examine the correlation between mild hyponatremia and sarcopenia, SMI, physical function test scores, and all the neuropsychological test scores. Cutoff scores for these dependent variables were based on the studies mentioned above. Covariates for both ANCOVA and the multiple regression model were selected based on previous studies.(4, 6, 10, 21) All analyses were performed using SPSS Statistics software (ver. 26 for Windows, Chicago, IL). A p-value < 0.05 was considered significant.

Results

During the study period, 7580 people aged ≥ 70 years visited the NCGG Memory Disorder Outpatient Center. Of them, 2961 met the inclusion criteria: 10 had moderate or more severe hyponatremia (SNa < 130 mEq/L), 75 had mild hyponatremia (SNa 130–135 mEq/L), 2872 had normonatremia (SNa 136–145 mEq/L), and 4 had hypernatremia (SNa > 145 mEq/L). Thus, 75 participants with mild hyponatremia and 2872 with normonatremia were included in this study.

The characteristics of hyponatremia and normonatremia are summarized for all participants in Table 1. The mild hyponatremia group was significantly older (median [interquartile range], 81.0 [76.0–84.0] vs 79.0 [75.0–83.0] years), had fewer women (46.7% vs 64.3%), had a lower Barthel Index score (100 [85.0–100.0] vs 100[95.0–100.0]), had a more history of cardiac disease (20.0% vs 11.7%), had more hearing problems (65.3% vs 52.1%), had higher diuretic use (9.3% vs 3.7%), and had higher potassium (4.4 [4.1–4.6] vs 4.1[3.9–4.4] mEq/L) compared with the normonatremia group. As shown in Table 2, the mild hyponatremia group also had more cases of sarcopenia, slower WS, shorter OLS time, and higher GDS-15 score.

Table 1
Participant characteristics

	n	Mild hyponatremia group	n	Normonatremia group	*p*
Age, years	75	81.0 (76.0–84.0)	2872	79.0 (75.0–83.0)	0.01
Female, n (%)	75	35 (46.7)	2872	1846 (64.3)	0.002
Education, years	73	9.0 (8.0–12.0)	2813	9.0 (9.0–12.0)	0.5
Barthel Index	75	100.0 (85.0-100.0)	2872	100.0 (95.0-100.0)	0.004
Heavy drinker*, n (%)	74	2 (2.7)	2840	55 (1.9)	0.6
Body mass index, kg/m^2	74	21.4 (19.4–23.6)	2861	21.9 (19.8–24.2)	0.3
History of cardiac disease, n (%)	75	15 (20)	2872	335 (11.7)	0.03
History of diabetes, n (%)	75	8 (10.7)	2872	205 (7.1)	0.2
History of liver disease, n (%)	75	1 (1.3)	2872	62 (2.2)	0.6
History of cancer, n (%)	75	9 (12)	2872	233 (8.1)	0.2
Joint pain, n (%)	75	28 (37.3)	2838	1161 (48.7)	0.5
Visual impairment, n (%)	75	39 (52.0)	2836	1588 (56.0)	0.5
Hearing impairment, n (%)	75	49 (65.3)	2837	1804 (52.1)	0.02
Diuretics use, n (%)	75	7 (9.3)	2872	107 (3.7)	0.01
CNS active drug use**, n (%)	75	28 (37.3)	2872	1117 (38.9)	0.8
Inactivity, n (%):	74	21 (28.4)	2824	945 (33.5)	0.4
Systolic BP, mmHg	70	149.0 (127.0-161.3)	2790	149.0 (134.0-166.0)	0.2
BNP, pg/mL	42	32.1 (18.6–70.0)	1503	31.6 (16.1–58.3)	0.3
eGFR, mL/min/1.73 m^2	75	69.6 (57.5–85.2)	2872	69.0 (56.0-73.5)	0.4
CRP, mg/dL	75	0.06 (0.03–0.2)	2872	0.05 (0.03–0.1)	0.1
Hemoglobin, mg/dL	75	13.2 (12.1–14.1)	2872	13.4 (12.5–14.3)	0.08
TSH, µlU/ml	75	1.6 (0.9–2.1)	2872	1.5 (1.0-2.2)	0.9

Values are median (interquartile range) or number (percentage). Differences were assessed using the Kruskal–Wallis test for continuous variables or the Chi-squared test for categorical variables. Abbreviations: BNP, brain natriuretic peptide; BP, blood pressure, CNS, central nervous system; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; TSH, thyroid stimulating hormone. *> 60 g/day of alcohol, **antiepileptic, antipsychotic, antidepressant and benzodiazepine drugs.

	n	Mild hyponatremia group	n	Normonatremia group	*p*
Potassium, mEq/L	75	4.4 (4.1–4.6)	2872	4.1 (3.9–4.4)	< 0.001

Values are median (interquartile range) or number (percentage). Differences were assessed using the Kruskal–Wallis test for continuous variables or the Chi-squared test for categorical variables. Abbreviations: BNP, brain natriuretic peptide; BP, blood pressure, CNS, central nervous system; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; TSH, thyroid stimulating hormone. *> 60 g/day of alcohol, **antiepileptic, antipsychotic, antidepressant and benzodiazepine drugs.

Table 2
Difference in physical and cognitive function between the groups

	n	Mild hyponatremia group	n	Normonatremia group	*p*
Sarcopenia, n (%)	41	25 (61.0)	1816	793 (43.7)	0.03
SMI, kg/m^2	48	6.3 (6.0–7.0)	2324	6.3 (5.7–7.1)	0.6
Physical function tests					
Grip strength, kg	37	18.6 (14.1–25.2)	1702	20.1 (15.7–25.5)	0.2
Walking speed, m/s	15	0.8 (0.5–0.9)	631	1.0 (0.8–1.2)	< 0.001
One-leg standing time, s	45	5.8 (2.6–13.3)	2259	9.0 (3.9–23.2)	0.02
Neuropsychological tests					
MMSE	75	20.0 (17.0–25.0)	2862	21.0 (17.0–25.0)	0.7
FAB	41	9.0 (7.0–12.0)	1699	10.0 (8.0–12.0)	0.6
Digit Span forward	44	5.0 (5.0–6.0)	1741	5.0 (5.0–6.0)	0.6
Digit Span backward	44	3.0 (3.0–4.0)	1728	3.0 (3.0–4.0)	0.9
Category fluency	73	8.0 (5.5–10.0)	2853	8.0 (6.0–10.0)	0.3
Logical memory Ⅱ	44	3.0 (3.0-12.5)	1743	3.0 (3.0–11.0)	0.2
GDS-15	72	5.0 (2.0–8.0)	2820	4.0 (2.0–6.0)	0.02

Values are median (interquartile range) or number (percentage). Differences were assessed using the Kruskal–Wallis test for continuous variables or the Chi-squared test for categorical variables. Abbreviations: FAB, Frontal Assessment Battery; GDS-15, 15-item Geriatric Depression Scale; MMSE, Mini–Mental state examination; SMI, skeletal muscle mass index.

ANCOVA showed that mild hyponatremia had a significant effect on SMI (F [1, 2199) = 6.2, p = 0.01) GS (F [1, 1627] = 7.1, p = 0.008) WS (F [1, 605] = 14.3, p < 0.001), OLS time (F [1, 2154] = 4.0, p = 0.049), and GDS-

15 score (F [1, 2689] = 5.0, p = 0.003) after controlling for covariates (Table 3).

Table 3
ANCOVA results for the comparison of skeletal mass index, physical function, and psychological tests between the groups

		Mild hyponatremia group		Normonatremia group			
	n	Adjusted mean ± SD	n	Adjusted mean ± SD	F	p	η^2
Skeletal muscle mass index, kg/m^2	43	6.5 ± 0.1	2178	6.7 ± 0.09	6.2	0.01[a]	0.003
Grip strength, kg	33	19.4 ± 1.3	1616	21.9 ± 1.0	7.1	0.008[a]	0.004
Walking speed, m/s	15	0.6 ± 0.09	612	0.9 ± 0.07	14.3	< 0.001[a]	0.03
One-leg standing test, s	42	4.9 ± 3.5	2134	10.0 ± 2.7	4.0	0.049[a]	0.002
Mini–Mental State Examination	67	21.4 ± 0.8	2655	20.9 ± 0.6	1.0	0.3[b]	< 0.001
Frontal Assessment Battery	39	9.7 ± 0.7	1610	9.4 ± 0.5	0.5	0.5[b]	< 0.001
Digit Span forward	42	5.4 ± 0.2	1647	5.3 ± 0.1	0.6	0.4[b]	< 0.001
Digit Span backward	42	3.3 ± 0.2	1633	3.2 ± 0.2	0.9	0.3[b]	0.001
Verbal fluency	66	2.9 ± 0.3	2651	2.7 ± 0.3	0.6	0.4[b]	< 0.001
Logical memory II	42	10.9 ± 3.6	1650	8.5 ± 2.7	0.8	0.4[b]	0.001
15-item Geriatric Depression Scale	66	4.9 ± 0.5	2644	4.1 ± 0.4	5.0	0.03[b]	0.002

η^2, the effect size

[a]Covariates adjusted for were age, sex, years of education, alcohol consumption, Barthel Index, body mass index, history of heart disease, diabetes, liver disease, cancer, and joint pain, visual impairment, hearing impairment, diuretics use, central nervous system active drug use, inactivity, hypotension, estimated glomerular filtration rate < 60, C-reactive protein, and Mini–Mental State Examination.

[b]Covariates adjusted for in model[a] excluded the Mini–Mental State Examination.

The results of multiple logistic regression using each cutoff score are shown in Table 4. After entering all variables selected from previous studies(10) into multivariable models 2 and 3, the elderly with mild

hyponatremia were significantly more likely to have weaker muscle strength as indicated by GS (odds ratio [OR]: 2.3, 95% confidence interval [CI]: 1.0–5.2; $p = 0.048$), poor physical performance as indicated by slower WS (OR: 7.6, 95% CI: 1.6–37.1; $p = 0.01$), impaired postural balance (OR: 2.1, 95% CI: 1.1–4.1, $p = 0.03$), and severe depressive mood (OR: 2.6, 95% CI: 1.2–5.7, $p = 0.001$). However, mild hyponatremia was not significantly associated with sarcopenia (OR:1.9, 95% CI: 0.9–4.0, $p = 0.09$) or lower SMI (OR: 1.7, 95% CI: 0.8–3.4, $p = 0.1$). There was no overfitting, and goodness of fit (Hosmer-Lemeshow test) indicated that each logistic model fit well.

Table 4
Results of logistic regression analysis for predicting sarcopenia, skeletal muscle mass, and physical and cognitive functions

Dependent variables	**Model 1**			**Model 2**		
	n	**OR (95% CI)**	p	**n**	**OR (95% CI)**	p
Sarcopenia	1857	1.9 (1.0-3.5)	0.06	1762	1.9 (0.9-4.0)	0.09
Low skeletal muscle mass index[a]	2372	1.8 (1.0-3.2)	0.05	2221	1.7 (0.8–3.4)	0.1
Low muscle strength[b]	1739	2.6 (1.2–5.8)	0.02	1649	2.3 (1.0-5.2)	0.048
Poor physical performance; Walking speed < 1 m/s	646	6.1 (1.3–28.6)	0.02	627	7.6 (1.6–37.1)	0.01
Impaired postural balance; One-leg standing test ≤ 5 s	2186	1.9 (1.0-3.6)	0.06	2059	2.1 (1.1–4.1)	0.03
Dependent variables	**Model 1**			**Model 3**		
	n	**OR (95% CI)**	p	**n**	**OR (95% CI)**	p
Cognitive disturbance; MMSE < 24	2879	0.9 (0.5–1.5)	0.6	2722	0.9 (0.5–1.6)	0.9
Executive dysfunction; FAB < 12	1719	0.8 (0.4–1.6)	0.5	1649	0.6 (0.3–1.3)	0.3
Poor walking memory; Digit Span forward < 6	1759	0.8 (0.4–1.6)	0.5	1689	0.9 (0.5–1.9)	0.8
Poor walking memory; Digit Span backward < 4	1746	0.8 (0.4–1.6)	0.6	1675	0.8 (0.4–1.6)	0.6
Poor attention; the category fluency subtest of the HDS-R < 6	1759	0.8 (0.8–0.9)	0.5	2717	0.7 (0.4–1.3)	0.2

Dependent variables	Model 1			Model 2		
Memory disorder[c]	1762	0.6 (0.3–1.1)	0.09	1691	0.6 (0.3–1.1)	0.1
Severe depression; GDS-15 ≥ 10	2856	2.7 (1.3–5.4)	0.005	2707	2.6 (1.2–5.7)	0.001
[a]Low skeletal muscle mass was defined as skeletal muscle mass index < 7.0 kg/m^2 in men and < 5.7 kg/m^2 in women						
[b]Reduced grip strength was defined as < 28 kg for men and < 18 kg for women						
[c]Raw WMS-R II score ≤ 8/9 for > 16 years of education, ≤ 4/5 for 8–15 years of education, ≤ 2/3 for 0–7 years of education						
Model 1. Adjusted for age and sex						
Model 2. In binary logistic regression analysis, all variables were entered into the multivariable model (age, sex, years of education, alcohol consumption, Barthel Index, body mass index > 25, body mass index < 18.5, history of heart disease, diabetes, liver disease, cancer, and joint pain, visual impairment, hearing impairment, diuretics use, central nervous system active drugs, inactivity, hypotension, estimated glomerular filtration rate < 60, C-reactive protein; and MMSE) using						
Model 3. In binary logistic regression analysis, all variables in Model 2 were entered into a multivariable model excluding the MMSE using						
Abbreviations: CI, confidence interval; FAB, Frontal Assessment Battery; GDS-15, 15-item Geriatric Depression Scale; HDS-R, Hasegawa Dementia Rating Scale-Revised; MMSE, Mini–Mental State Examination; OR, odds ratio; WMS-R, Wechsler Memory Scale-Revised						

Discussion

Correlation between mild hyponatremia and SMM and physical function

The mild hyponatremia group had significantly lower SMI, weaker GS, slower WS, and shorter OLS time than the normonatremia group, even after controlling for covariates. When using the AWGS criteria for sarcopenia, the mild hyponatremia group had a significantly higher risk of worse physical performance and impaired balance, and a marginally significant higher risk of worse muscle strength, but was not at risk of developing sarcopenia or having a lower SMI.

Previous studies demonstrated that chronic hyponatremia causes gait disturbances in both rats(5) and humans.(2) This study demonstrated that even mild hyponatremia was associated with gait disturbances and balance impairment. The mechanism behind these observations is yet to be determined. However, for the mechanism whereby hyponatremia contributes to gait dysfunction and balance impairment, if we

look at it from the viewpoint of the CNS, the brain cells adapt to hyponatremia by swelling with the loss of osmolytes, such as glutamate,(22) which is a neurotransmitter involved in gait and balance function.(4) Rerelease of glutamate from the cytosol to extracellular space contributes to excessive activation of neuronal glutamate receptors, causing excitotoxic cell damage and death in the CNS.(23) However, it remains to be elucidated what severity of hyponatremia, and particularly whether mild hyponatremia, causes these consequences, which could lead to slow WS and balance dysfunction.

On the other hand, we found that muscle strength as measured by GS was significantly different between the mild hyponatremia and normonatremia groups of elderly participants, but when using the AWGS cutoff value for sarcopenia, the logistic regression model showed that the association between mild hyponatremia and GS was marginal. While Cairns et al. observed a 10% decrease in muscle strength when the sodium concentration was decreased from 147 to 60 mmol/L in mice,(24) Vandergheynst et al. did not observe any significant difference in GS when the sodium concentration was increased from 127.7 ± 2.5 mmol/L to 136.1 ± 1.8 mmol/L in humans.(25) Mild hyponatremia itself is correlated with muscle strength but the level of hyponatremia may be more severe, noticeably lower than the cutoff.

Our study revealed that elderly with even mild hyponatremia had poor physical function. A previous study reported that elderly patients with similar severity of hyponatremia were much more sensitive to alterations to gait tests than younger patients.(26) These findings imply elderly people with even mild hyponatremia may be at risk of physical dysfunction.

It is of particular important for clinical practice to know that the elderly with mild hyponatremia had low physical function, because hyponatremia could be treatable. Vandergheynst et al. reported that correction of chronic mild-to-moderate hyponatremia improved nerve conduction velocity and F-wave latencies.(25) Another study reported a significant improvement in activity of daily living and cognition among effectively treated hyponatremia geriatric patients.(27) Thus, mild hyponatremia in the elderly deserves more of our attention. Additional longitudinal studies are needed to strengthen the evidence on the severity of hyponatremia that affects physical function in the elderly and the underlying mechanism.

Regarding low muscle mass in elderly with mild hyponatremia, hyponatremia tended to lead to progressive SMM loss in rats.(7) Hyponatremia has also been often observed in patients who are malnourished and in the elderly with sarcopenia.(28) In the present study, although there was no significant difference in BMI between the elderly with mild hyponatremia and the elderly with normonatremia, those with mild hyponatremia might have had low protein intake and/or vitamin D deficiency. However, the impact of these factors on muscle strength may be insufficient to bring the SMI score under the cutoff point for mild hyponatremia.

Association between mild hyponatremia and depressive mood

This study also found that mild hyponatremia was associated with depressive mood, but not with other neuropsychological tests scores. To our knowledge, this study is the first to report an association between

mild hyponatremia and depressive mood in the elderly. Previously, the efficacy of tolvaptan was evaluated in patients with hyponatremia. Serum sodium concentrations increased more in the tolvaptan group than in the placebo group and a significant improvement on Mental Component Summary (for vitality, social functioning, emotionally limited accomplishment, calmness, and sadness) of the Medical Outcomes Study 12-item Short-Form General Health Survey in tolvaptan group was demonstrated. (29)The mechanism has yet to be determined, but some studies have suggested a correlation between depression and glutamate, whose release from brain cells to the extracellular space may be mediated by hyponatremia. For example, decreased glutamate levels were reported in white matter in adults with major depression.(30) Also, plasma levels of glutamate (i.e., extracellular glutamate) in patients with depression have been reported to be higher than those in normal controls.[31] Anti-glutamate agents are known to have antidepressant effects in patients with depression.(32) Glutamates, which are released from brain cells to outside the cell might lead to depressive mood. Alternatively, elderly with depressive mood might not have sufficient appetite to ingest enough dietary sodium.

Study strengths and limitations

This study used detailed neuropsychological test results and is the first to reveal a correlation between mild hyponatremia and depressive mood. A second strength of the study is its large sample, so many possible confounders could be minimized, including pseudohyponatremia, renal dysfunction, and acute infection. However, there are also some limitations. We did not determine the causes or chronicity of mild hyponatremia. The duration of hyponatremia or severity of comorbidities may be an additional risk for physical dysfunction or depressive mood. In addition, this is a cross-sectional study and the specific mechanisms underlying the association between mild hyponatremia and physical function and depressive mood remain to be investigated.

Conclusions

In this study, elderly participants with mild hyponatremia had impaired lower skeletal muscle mass, physical function and depressive mood compared with elderly participants with normonatremia. Mild hyponatremia in the elderly deserves more attention than it currently receives. Additional longitudinal studies are needed to strengthen the evidence on the severity of hyponatremia that affects physical and cognitive function in the elderly.

Abbreviations

BW: body wight, CI: confidence interval, CNS: central nervous system, FAB: Frontal Assessment Battery, GDS-15, 15-item Geriatric Depression Scale, OLS: one-leg standing, OR: odds ratio, MMSE: Mini–Mental State Examination, SMI: Skeletal muscle mass index, WMS-R: Wechsler Memory Scale-Revised, WS: walking speed

Declarations

Ethic approval and consent to participate

This study was approved by an ethics committee of Japan's National Center of Geriatrics and Gerontology. (No.1415) Written informed consent was obtained from all subjects or their legally authorized representatives prior to enrollment in the study.

Consent for publication

Not applicable.

Availability of data and materials

The data supporting the conclusion of this article may be available from the corresponding author upon reasonable request.

Competing Interests

All of authors declare that have no competing interests.

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Authors' contributions

CF, HF and YS formed the research question. Taiki S coded the data, and CF conducted the analyzed with SS, TS and CHH and providing input on the analysis. CF wrote the article. UH, KM, TK and Takashi S reviewed the article. All authors approved the final draft.

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