Liu Taiwan	• Muscle mass by DXA (GE Healthcare, Madison, WI, USA) • Handgrip strength by a dynamometer (Smedlay's Dynamo Meter; TTM, Tokyo, Japan; 3 trials for the dominant hand, using the highest reading) • GS: 6-m walk	**ASM/ht^2:** 1st quintile of study population **Handgrip strength & GS:** 1st quintile of study population	**Muscle mass index:** 7.0 kg/m^2 in men, 5.9 kg/m^2 in women **Handgrip strength:** 25 kg in men, 16 kg in women **GS:** 1.0 m/s in men, 0.9 m/s in women	9.4% in men, 9.8% in women	481 aged ≥65 years, male 55.5%	–	10
Wu Taiwan	• Muscle mass by BIA (Tanita BC-418; Tanita, Tokyo, Japan) • Handgrip strength (Grip-D, TKK 5401, Japan; 2 trials for both hands, using the highest reading) • GS: 15-ft walking test	**Total muscle mass/ ht^2:** mean – 2SD of young adults[8] **Handgrip strength:** EWGSOP cut-off **GS:** EWGSOP cut-off	**Muscle mass index:** 7.70 kg/m^2 in men, 5.67 kg/m^2 in women **Handgrip strength:** Men: BMI ≤24 kg/m^2, 24.1~28 kg/m^2 and >28 kg/m^2 were ≤29 kg, ≤30 kg and ≤32 kg Women: BMI≤23 kg/m^2, 23.1~26 kg/m^2, 26.1~29 kg/m^2 and >29 kg/m^2 were ≤17 kg, ≤17.3 kg, ≤18 kg and ≤21 kg **GS:** ≤0.8 m/sec	Sarcopenia, 7.1%, Severe sarcopenia, 5.6%	Total 549 study subjects, 285 male and 264 female aged ≥ 65 years Mean age: 76.0 ± 6.2 years	–	11
Kim Korea	• Muscle mass by DXA (Discovery-W, Hologic, Bedford, MA)	**Muscle indices:** ASM/ht^2 and ASM/Wt: mean – 2SD of young adults or <1st quintile of total body skeletal muscle mass/weight **(TSM/Wt)** from control subjects	**ASM/ht^2:** 7.40 kg/m^2 in men, 5.14 kg/m^2 in women **ASM/Wt:** 29.5% in men, 23.2% in women **TSM/Wt:** 34.9% in men, 25.8% in women	–	414 adults aged ≥65 years Mean age: men 70.6 years and women 70.9 years	**ASM/ht^2:** young healthy volunteers, aged 20–40, *n* = 145 (54 men, 91 women) **ASM/Wt:** 2392 healthy adults aged 20–40 years (1054 men, 1338 women)	12
Ishii Japan	• Muscle mass by BIA (Inbody 430, Biospace, Seoul, Korea) • Handgrip strength by a grip strength dynamometer (Takei Scientific Instruments, Niigata, Japan)[2 trials for dominant hand, using the higher reading] • GS: middle 5 m over an 11-m straight course at their usual speed	**ASM/ht^2:** mean – 2SD of young adults[13] **Handgrip strength:** 1st quintile of study population **GS:** 1st quintile of study population	**Muscle mass index:** <7.0 kg/m^2 in men, <5.8 kg/m^2 in women **Handgrip strength:** 30 kg in men, 20 kg in women **GS:** ≤1.26 m/s	14.2% in men, 22.1% in women	1971 functionally independent, community-dwelling adults aged ≥65 years 977 men, 994 women	–	14
Sampaio Japan	• Muscle mass by BIA (Inbody 430; Biospace, Seoul, Korea) • Handgrip strength using a dynamometer (Smedlay's Dynamo Meter, TTM, Tokyo, Japan; 1 trial for each hand, using the higher reading) • GS: 10-m walking in a 12-m length	**Total muscle mass/ht^2:** 1st quintile of study population	**Total muscle mass/ht^2:** 8.81 kg/m^2 in men, 7.57 kg/m^2 in women	–	Community-dwelling Japanese older adults (*n* = 175; male = 84, female = 91)	–	15

Table 1 *Continued*

1st Author and nationality	Available measurements	Cut-off definition	Cut-off values	Prevalence of sarcopenia	Research population	Reference population	Ref. no.
Shimokata, Japan	• Muscle mass by DXA (QDR-4500; Hologic, Bedford, MA, USA) • Leg extension power measured using the T.K.K.4236 adjustable seat and foot plate (Takei, Niigata, Japan; the maximum values of 8 tests were analyzed) • Grip strength was measured using the T.K.K.4301 (Takei; maximum values of 2 tests for dominant hand were analyzed)	**ASM/ht^2:** mean − 2SD of young adults[16]	**ASM/ht^2:** <6.87 kg/m^2 in men <5.46 kg/m^2 in women	The prevalence of low muscle mass: 27.1% in men 16.4% in women	NILS-LSA 1090 men, mean age 59.3 ± 11.0 years 1081 women, mean age 59.3 ± 10.9 years	–	17
Yamada Japan	• Muscle mass by BIA (Inbody 720; Biospace, Seoul, Korea)	**ASM/ht^2:** 1st quintile of study population	**ASM/ht^2** **For men** 65–69; 7.06 kg/m^2 70–74; 7.09 kg/m^2 75–79; 6.83 kg/m^2 65–79; 7.02 kg/m^2 **For women** 65–69; 5.61 kg/m^2 70–74; 5.63 kg/m^2 75–79; 5.54 kg/m^2 65–79; 5.61 kg/m^2	–	Community healthy men (n = 16 379) and women (n = 21 660) aged 40–79 years Mean age: 54.5 ± 9.9 years, 56.9% women	–	18
Yoshida Japan	• Muscle mass by BIA (MC-980A; Tanita, Tokyo, Japan) • Handgrip strength by a hand dynamometer Grip-D (Takei; 1 trial for the dominant hand) • GS: middle 2.4 m in a 6.4 m walking at their usual pace for five times, using the average value	**ASM/ht^2 and Handgrip strength:** sex-specific 1st quintile of study population **GS:** EWGSOP cut-off	**ASM/ht^2:** 7.09 kg/m^2 in men, 5.91 kg/m^2 in women **Handgrip strength:** 28.8 kg in men, 18.2 kg in women **GS:** ≤0.8 m/s	age ≥65 years: 8.2% in men and 6.8% in women) age ≥80 years: 25.0% in men and 12.2% in women	4811 people aged 65 years and over, 48.7% men: (n = 2343, mean age 72.2 ± 5.5 years) women: (n = 2468, mean age 72.1 ± 5.7 years)	–	19
Yu Hong Kong	• Muscle mass by DXA (Hologic Delphi W4500 densitometer; Hologic, Bedford, MA, USA) • Grip strength using a dynamometer (JAMAR Hand Dynamometer 5030JO; 2 trials for each hand, using the average value between right and left hand) • Walking speed: a 6-m walking speed (2 trials, using best time recorded)	**ASM/ht^2:** 1st quintile of study population **Handgrip strength:** 1st quintile of study population **GS:** EWGSOP cut-off	**ASM/ht^2** <6.52 kg/m^2 in males <5.44 kg/m^2 in females **Handgrip strength:** ≤28 kg in males ≤18 kg in females **GS** ≤0.8 m/s	361 (9.0%)	4000 community-dwelling men and women aged 65 years and above, men 50% Mean age: 72.5 ± 5.2 years	–	20

ASM, appendicular skeletal mass; BIA, bioelectrical impedance analysis; BMI, body mass index; DXA, dual X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; FFM, fat free mass; GS, gait speed; QS, quadriceps strength; RASM, relative appendicular skeletal muscle mass; SMI, skeletal muscle index.

Table 2 Comparison of diagnostic algorithm of sarcopenia among Asian Working Group for Sarcopenia, European Working Group on Sarcopenia in Older People, and International Working Group on Sarcopenia

	AWGS	EWGSOP	IWGS
Target for screening	Community-dwelling older adults and older people with certain clinical conditions, such as presence of recent functional decline or functional impairment, unintentional body weight loss for over 5% in a month, depressive mood or cognitive impairment, repeated falls, malnutrition, chronic conditions, such as chronic heart failure, chronic obstructive lung disease, diabetes mellitus, chronic kidney disease, connective tissue disease, tuberculosis infection, and other chronic wasting conditions	Community-dwelling people aged ≥65 years	Individuals with functional decline, mobility-related difficulties, history of recurrent falls, recent unintentional body weight loss, post-hospitalization, and chronic conditions, such as type 2 diabetes, congestive heart failure, chronic kidney disease, chronic obstructive lung disease, rheumatoid arthritis, and cancer
Target age group	≥60 years or ≥65 years depending on the definition of older adults in each country	≥65 years	Not specified
Screening	Gait speed and handgrip strength	Gait speed	Gait speed
Cut-off of gait speed	0.8 m/s	0.8 m/s	1.0 m/s
Cut-off of handgrip strength	26 kg in men and 18 kg in women	30 kg in men and 20 kg in women	NA
Cut-off of muscle mass (appendicular muscle mass/ht^2)	7.0 kg/m^2 in men and 5.4 kg/m^2 in women by DXA, 7.0 kg/m^2 in men and 5.7 kg/m^2 in women by BIA	Mean − 2SD of young adults	7.23 kg/m^2 in men and 5.67 kg/m^2 in women

AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance analysis; BMI, body mass index; DXA, dual X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; IWGS, International Working Group on Sarcopenia.

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Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Association between serum uric acid and lumbar spine bone mineral density in peri- and postmenopausal Japanese women

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Abstract
Summary Previous studies on the association between uric acid and bone mineral density yielded conflicting results. In this study, we demonstrated positive association between uric acid and lumbar spine bone mineral density in peri- and postmenopausal Japanese women. Further research is needed to elucidate the underlying mechanism.
Introduction Oxidative stress has been implicated in the pathogenesis of osteoporosis. Uric acid, a potent antioxidant substance, has been associated with bone mineral density but previous studies have yielded conflicting results. The objective of the study was to examine the association between serum uric acid and lumbar spine bone mineral density (BMD).
Methods This was a retrospective analysis of medical records of 615 women, aged 45–75 years, who had lumbar spine BMD measurement by dual-energy X-ray absorptiometry as a part of health checkup from August 2011 to July 2012.
Results Mean serum uric acid level was 4.7 mg/dL. Serum uric acid level was positively and significantly associated with lumbar spine BMD independent of age, body mass index, smoking, drinking, physical activity, years after menopause, diabetes mellitus, hypertension, serum calcium, estimated glomerular filtration rate, plasma C-reactive protein, and serum alkaline phosphatase (standardized beta=0.078, $p=0.049$). Uric acid rapidly increased until the age of 60 years, and then decelerated but continued to increase thereafter. The association between lumbar spine BMD and uric acid remained significantly positive after excluding women older than 60 years.
Conclusion The present study showed that higher uric acid levels were linearly associated with higher lumbar spine BMD in peri- and postmenopausal Japanese women. Further research is needed to elucidate the underlying mechanism of the association between uric acid and BMD.

Keywords Bone mineral density · Menopause · Osteoporosis · Uric acid

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Introduction

Osteoporosis, a disease characterized by bone fragility and increased risk of fracture, has been chiefly attributed to the decline of ovarian function at menopause and resulting sex steroid deficiency [1]. On the other hand, oxidative stress has also been implicated in the pathogenesis of osteoporosis [1–12]. For example, observational studies suggested that a higher intake of the antioxidant vitamin C was associated with slower decline of bone mineral density (BMD) [10] and lower risk of hip and nonvertebral fractures [9], and that diminution in plasma antioxidant activity or high oxidative stress was observed in patients with osteoporosis compared with those without [4, 6, 8, 11, 12].

In agreement with accumulating evidence supporting the role of oxidative stress as one of the underlying mechanisms of osteoporosis, uric acid, a potent antioxidant substance [13], has been associated with osteoporosis. In a large population-based, cross-sectional study on older men, higher serum uric acid levels were significantly associated with higher BMD at

various sites including the lumbar spine and femoral neck, adjusting for covariates [14]. Higher serum uric acid levels were also associated with a lower prevalence of osteoporosis, vertebral fracture ascertained by lateral spine scans, and history of nonvertebral fracture [14]. Another large cross-sectional study replicated the association of uric acid positively with BMD and negatively with lower prevalence of vertebral fracture in postmenopausal women [15]. This study also demonstrated that uric acid suppressed osteoclastogenesis and reduced the production of reactive oxygen species in osteoclast precursors, providing important evidence that the positive association between uric acid and bone mineral density may be related to the antioxidant effect of uric acid. Moreover, in a longitudinal study on peri- and postmenopausal female twins, higher uric acid levels at baseline were associated with higher BMD at baseline and a slower rate of decline in BMD thereafter, independent of covariates [16].

However, there is also strong evidence linking hyperuricemia with increased risk of cardiovascular disease [17, 18] in which oxidative stress plays an important pathophysiological role [19, 20]. One of the proposed hypotheses explaining this paradox is related to a shift in the prooxidant/antioxidant properties of uric acid depending on its concentration. Experimental studies suggested that uric acid may become prooxidant under certain conditions [21, 22], particularly when it is supersaturated in blood. Therefore, it is conceivable that uric acid may confer protective antioxidant effects or detrimental prooxidant effects when, respectively, present at normal levels or at supersaturated concentrations [23]. One cross-sectional study on young men and women actually demonstrated that *higher* levels of serum uric acid were associated with *lower* BMD at the femoral neck in women after controlling for age, weight, and serum creatinine [24]. Interestingly, uric acid levels in most female participants were within the normal range. Estrogen has an antioxidant property [1] and also reduces serum uric acid by enhancing renal clearance [25]. Therefore, the finding of an inverse association between estrogen and uric acid may be attributable to the confounding effects of estrogen, considering that the women in this study were predominantly premenopausal. However, the effects of age and menopause on the association between uric acid and osteoporosis have not been empirically examined, and further research is needed.

In the present study, we examined the association between uric acid and BMD in peri- and postmenopausal Japanese women. We hypothesized that BMD and uric acid are linearly and positively associated independent of covariates including the menopausal status in the normal range of serum uric acid, but the association becomes inverse in the hyperuricemic range.

Methods

Subjects

This was a retrospective analysis of medical records obtained from Kanto Central Hospital which is a 470-bed urban teaching hospital in Tokyo funded and run by the Mutual Aid Association of Public School Teachers. Teachers who work at public schools and belong to the Association have health checkup annually at the Center for Health Check-up and Preventive Medicine of the Hospital since workers are required by law to have annual health checkup regardless of their age in Japan. Health checkup is performed in a standardized manner, consisting of consultation with a doctor, height and weight measurement, laboratory tests, and several studies including chest X-ray. Lumbar spine BMD measurement by dual-energy X-ray absorptiometry (DXA) is offered optionally for teachers with financial subsidy from the association.

We drew data from the medical records of 3,814 women aged between 45 and 75 years who received a health checkup at the Center from August 2011 to July 2012. Of the women, 638 (16.7 %) out of 3,814 had lumbar spine BMD measurement. Women with chronic kidney disease (estimated glomerular filtration rate (GFR) lower than 60 mL/min/1.73 m^2) ($n=10$) or who had received treatment for osteoporosis ($n=8$) were excluded from the analysis. Those who had received treatment for either hypothyroidism ($n=4$) or hyperthyroidism ($n=1$) were also excluded because of the effect of thyroid hormones on bone [26]. No women received oral steroids, loop diuretics, high-dose thiazide diuretics, hormone replacement therapy, or treatment for hyperuricemia or chronic liver disease. After exclusion, 615 women were included in the analysis. This study was approved by the Ethics Committee of Kanto Central Hospital.

Measurements

Standardized interviews and self-reported questionnaires were used to obtain the following information: age (years), smoking habit (current smoker, past smoker, or never smoked), drinking habit [abstainer, infrequent (non-abstainer but one or less drink per week), and light (more than one drink per week but one or less per day), or moderate to heavy (more than one drink per day)], physical activity (any regular exercise or none), age at menopause, medical history, and use of prescription medication. Height and weight were measured using a fixed stadiometer and a digital scale, with the participant wearing light clothing. Body mass index (BMI) was calculated from weight and height.

Fasting blood samples were collected from each participant, and serum uric acid, creatinine, calcium, and alkaline phosphatase were measured using a standard technique with a medical autoanalyzer (BioMajesty JCA-BM2250). The assay

range for serum uric acid was 0.2–200 mg/dL. Plasma C-reactive protein (CRP) was measured using a latex immunoassay with the assay range of 0.2–4,000 mg/L. Estimated GFR was calculated from age, sex, and serum creatinine [27].

Subjects with a reported history of diabetes mellitus, fasting glucose of 126 mg/dL or higher, or glycosylated hemoglobin levels at 6.5 % or higher were classified as diabetic. Those with a reported history of hypertension, systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher were classified hypertensive.

Bone mineral density measurements

BMD of the lumbar spine was measured by DXA using a GE Lunar Prodigy. A standard quality control program included daily calibrations with machine-specific phantoms to ensure machine accuracy of greater than 98 %.

Statistical analysis

Uric acid becomes insoluble and supersaturated in bodily fluids above a concentration of about 7 mg/dL. The nonparametric locally weighted scatterplot smoothing (LOESS) method was used to determine whether the saturation point affects the functional form of the association between uric acid and BMD. The LOESS method generated a smooth curve of BMD as a function of uric acid. Visual inspection of the LOESS plot indicated that the relationship between BMD and uric acid was piecewise linear with an inflection (change of slope) at the uric acid value of 4.8, above which the slope appeared steeper (Fig. 1). We then fitted piecewise linear spline models to BMD as a function of uric acid with a fixed knot at 4.8. We also employed generalized additive models to examine the shape of the association between uric acid and BMD accounting for other covariates. The generalized additive model is an extension of the generalized linear model in which one or more independent variables can be modeled with nonparametric smooth functions [28].

The model was initially adjusted for age and BMI (model 1). Covariates for lifestyle risk factors for osteoporosis including physical activity; smoking and drinking habit; years after menopause (coded as 0 if subject had not experienced menopause) (model 2); comorbidity including diabetes mellitus and hypertension (model 3); and serum calcium, alkaline phosphatase (ALP), estimated GFR, and log (CRP) (model 4) were successively added to regression models. The selection of covariates was based on the literature review on factors affecting BMD [29–35].

There were missing values for physical activity in 180 women (29.3 %), years after menopause in 140 women (22.8 %), and drinking habit in 1 woman (0.2 %). These were imputed using the expectation–maximization (EM) algorithm [36].

Statistical analyses were performed using SAS, version 9.2 (SAS Institute, Inc., Cary, NC, USA) and R statistical software

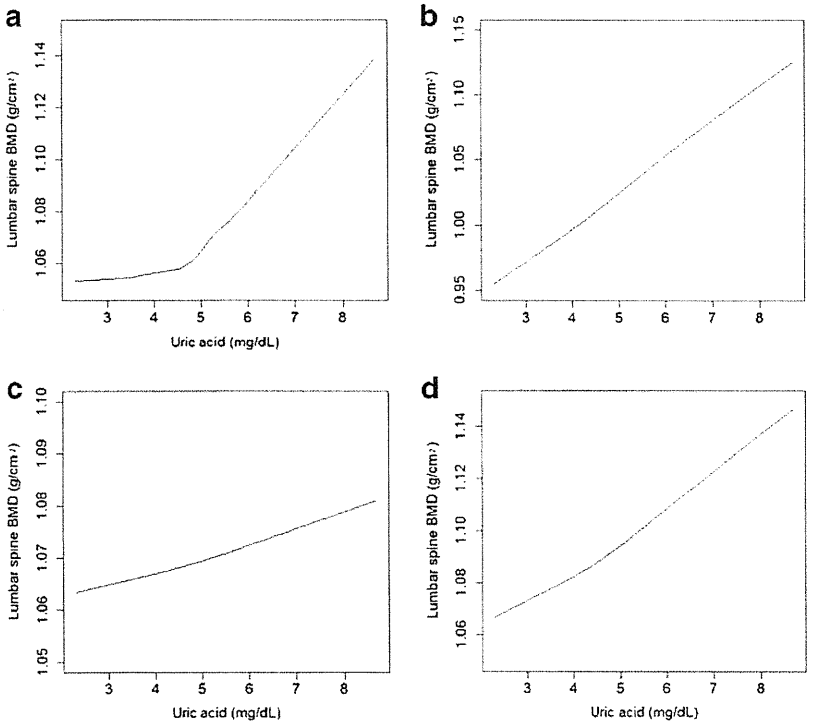

Fig. 1 Plots of lumbar spine bone mineral density against uric acid level. **a** The LOESS plot. **b**–**d** The plots generated using generalized additive models accounting for age (**b**), body mass index (**c**), or estimated glomerular filtration ratio (**d**). The values of the covariates were fixed at their mean when the association between lumbar spine BMD and uric acid were plotted. *BMD* bone mineral density

version 2.15.2 (R Foundation, Vienna, Austria). All statistical tests were two-sided, and a p value less than 0.05 was considered statistically significant.

Results

Characteristics of study participants are shown in Table 1. Women included in the analysis were similar to those excluded from the analysis with respect to major characteristics. Of the 615 women included in the analysis, serum uric acid had a mean value of 4.7 mg/dL with standard deviation of 1.0 mg/dL. Only 12 women (2.0 %) had hyperuricemia (i.e., uric acid level higher than 7.0 mg/dL), and 19 (3.1 %) women were obese (i.e., BMI equal to or higher than 30 kg/m^2).

Table 1 Characteristics of participants

	Participants (n=615)
Uric acid (mg/dL)	4.7±1.0
Lumbar spine bone mineral density (g/cm^2)	1.06±0.18
Age (years)	57.6±6.4
Log (CRP in mg/L)[a]	0.12±0.17
BMI (kg/m^2)	22.2±3.5
Smoking	
Current	19 (3.1)
Ex	53 (8.6)
Never	543 (88.3)
Drinking[b]	
Abstainer	219 (35.7)
Infrequent	188 (30.6)
Light	171 (27.9)
Moderate to heavy	36 (5.9)
Activity[b]	
Sedentary	283 (65.1)
Active	152 (34.9)
Postmenopausal[b]	373 (78.5)
Age at menopause in postmenopausal women (years)	50.9±3.8
Diabetes	44 (7.2)
Hypertension	114 (18.5)
Serum calcium (mg/dL)	9.3±0.3
Estimated GFR (mL/min/1.73 m^2)	97.8±21.6
ALP (IU/L)	223.5±66.3

For continuous variables, the mean is shown with standard deviation. For categorical variables, the number (percentage) is shown. Percentages may not add up to 100 because of rounding errors

BMD bone mineral density, *CRP* C-reactive protein, *BMI* body mass index, *GFR* glomerular filtration rate, *ALP* alkaline phosphatase, *IU* international unit

[a] The natural log (base e) was taken for CRP due to skewed distribution

[b] There were missing values for physical activity in 180 women (29.3 %), years after menopause in 140 women (22.8 %), and drinking habit in 1 woman (0.2 %)

Association between BMD and uric acid

In piecewise linear regression of BMD as a function of uric acid with a fixed knot at uric acid level of 4.8 mg/dL, the change in slope at the knot was not statistically significant in univariate analysis and all four models of multivariate analyses (p values=0.31–0.79). The generalized additive models also demonstrated that uric acid was approximately linearly associated with BMD when accounting for each of age, BMI, or estimated GFR (Fig. 1). Therefore, the knot was subsequently dropped. The resulting multiple linear regression models fitted simple linear relationship between uric acid and BMD. Serum uric acid levels were significantly and positively associated with lumbar spine BMD adjusting for age and BMI (model 1, Table 2). The association between uric acid and BMD remained significant after successively adjusting for lifestyle risk factors and years after menopause (model 2); comorbidity (model 3); and serum calcium, estimated GFR, log (CRP), and ALP (model 4). Serum uric acid levels explained 0.48–0.63 % of variance in BMD (R^2=0.187–0.258).

Effect modification

One of the presumed mechanisms of the association between BMD and uric acid is the antioxidant property of uric acid. Considering the complicated and interrelated relationship between oxidative stress and inflammation, we postulated that the degree of inflammation modifies the association between BMD and uric acid. To test this hypothesis, we examined the interaction between log (CRP) and uric acid, but it was not significant (p=0.22).

Table 2 Adjusted associations of serum uric acid with lumbar spine bone mineral density (n=615)

	Beta[a]	%V[b]	p	R^2
Model 1	0.084	0.63	0.03	0.187
Model 2	0.081	0.57	0.04	0.199
Model 3	0.084	0.61	0.03	0.206
Model 4	0.078	0.48	0.049	0.258

Model 1—adjusted for age, BMI; model 2—adjusted for age, BMI, smoking, drinking, physical activity, and years after menopause; model 3—adjusted for age, BMI, smoking, drinking, physical activity, years after menopause, diabetes, and hypertension; model 4—adjusted for age, BMI, smoking, drinking, physical activity, years after menopause, diabetes, hypertension, serum calcium, estimated GFR, log (CRP), and ALP. Abbreviations are as in Table 1

[a] Standardized beta coefficient

[b] Variance of lumbar spine bone mineral density explained by uric acid

Sensitivity analysis

Previous studies have demonstrated that menopause is associated with changes in both BMD and uric acid. Women have a minimal decline in BMD until 1–2 years prior to the final menstrual period when they begin to experience a rapid decline in BMD. The decline in BMD decelerates 1–2 years after the final menstrual period, but continues [37]. On the other hand, postmenopausal status was associated with higher levels of uric acid [38, 39]. Therefore, the associations of age with BMD and uric acid in this study sample of peri- and postmenopausal women may not be linear. The LOESS plots of BMD and uric acid as a function of age demonstrated that both of the relationships were piecewise linear, with an inflection at around the age of 60 (Fig. 2a, b). Uric acid rapidly increased with increasing age until age 60 years, then decelerated but continued to increase. Similarly, lumbar spine BMD declined rapidly with increasing age, but the rate of decline slowed down at the age of 60 years but continued to decline. As a sensitivity analysis, we examined the association between uric acid and BMD after excluding 177 women older than 60. The analysis demonstrated significant and positive associations between BMD and uric acid in all models, with effect sizes slightly larger than those observed in the main analyses, supporting the robustness of our scientific conclusion (Table 3).

We also conducted another sensitivity analysis after excluding 281 women with any missing values in covariates. This sensitivity analysis revealed slightly larger effect sizes of the association between UA and BMD than those in the main analyses, but the associations failed to reach statistical significance (data not shown).

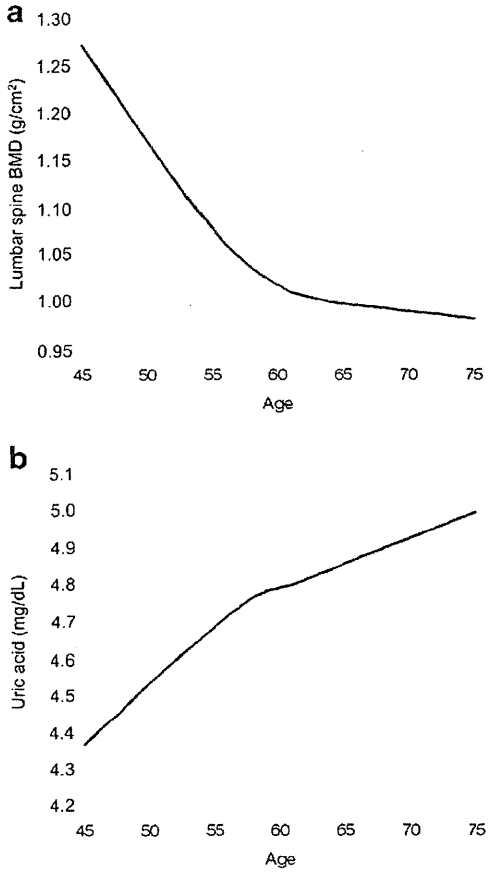

Fig. 2 LOESS plots of bone mineral density and uric acid against age. *BMD* bone mineral density

Discussion

In this cross-sectional analysis of 615 peri- and postmenopausal women aged between 45 and 75 years, higher serum levels of uric acid were significantly associated with higher values of BMD in the lumbar spine, independent of covariates including years after menopause. One standard deviation (1.0 mg/dL in this study population) increment in uric acid was associated with an approximately 0.08 standard deviation increase in lumbar spine BMD. We also demonstrated rapid changes in uric acid and BMD with increasing age until the age of 60, and the rate of changes slowed down thereafter. The positive association between BMD and uric acid remained significant after excluding women older than 60 years.

Our study confirms and extends a previous study that has demonstrated a positive association between BMD and uric acid in peri- and postmenopausal women [15, 16]. We showed that uric acid was positively and linearly associated with lumbar spine BMD, and therefore not only the presence of hyperuricemia but also the magnitude of uric acid elevation plays an important role. Addition of years after menopause did not significantly affect the uric acid–BMD association. We did not observe any sharp inflection point (i.e., change of slope) in the association between uric acid and BMD, incongruent with our hypothesis that the association between uric acid and

Table 3 Adjusted associations of serum uric acid with lumbar spine bone mineral density after excluding 177 women older than 60 years ($n = 438$)

	Beta[a]	%V[b]	p	R^2
Model 1	0.103	0.96	0.02	0.284
Model 2	0.091	0.73	0.04	0.294
Model 3	0.101	0.89	0.02	0.304
Model 4	0.107	0.91	0.02	0.359

Model 1—adjusted for age and BMI; model 2—adjusted for age, BMI, smoking, drinking, physical activity, and years after menopause; model 3—adjusted for age, BMI, smoking, drinking, physical activity, years after menopause, diabetes, and hypertension; model 4—adjusted for age, BMI, smoking, drinking, physical activity, years after menopause, diabetes, hypertension, serum calcium, estimated GFR, log (CRP), and ALP. Abbreviations are as in Table 1

[a] Standardized beta coefficient

[b] Variance of lumbar spine bone mineral density explained by uric acid

BMD becomes inverse in the hyperuricemic range. However, it should be noted that only a small portion of women in this study had hyperuricemia, and further study is needed to determine if the association between BMD and uric acid in the hyperuricemic range may differ from that in the physiologic range.

We also demonstrated that there was a period of rapid increase in uric acid until the age of 60 years when the rate of increase slowed. The observed trajectory of uric acid is consistent with menopause-related changes, rather than changes secondary to chronological aging. This is congruent with previous studies showing that uric acid levels were higher in postmenopausal women compared with pre- or perimenopausal women [38, 39]. We observed a similar menopause-related change in BMD, consistent with previous studies [37]. However, the inflection (i.e., change of slope) was observed at around the age of 60 for both uric acid and BMD in the present study, which appears too far apart from the mean age at menopause of approximately 51 years. The possible explanations for the discrepancy include reporting error and the nature of cross-sectional data, which are predisposed to recall bias and are unable to separate the effects of aging from secular trend. Hence, a longitudinal study is warranted to determine the precise trajectory of uric acid during the menopause transition.

This study has several limitations. First, the study design was cross-sectional and did not allow us to infer a cause–effect relationship between uric acid level and BMD. However, one previous longitudinal study demonstrated that higher serum uric acid levels were associated with slower annual decline in BMD in peri- and postmenopausal women [16]. Second, we employed an EM algorithm to impute missing values in covariates. Missing values occurred mostly in two variables—physical activity and age at menopause. Sensitivity analysis excluding women with any missing values in covariates yielded similar, albeit not significant, effect sizes of the association between BMD and uric acid, indirectly supporting the robustness of the approach. The association failed to reach statistical significance due to the reduced number of women included in the sensitivity analysis. Third, the data were obtained from the medical records of female teachers who had received health checkup annually and were therefore expected to be generally in good health and health conscious. In fact, the prevalence of comorbidity such as hypertension and diabetes, and the smoking rate were lower than those in the general population [40–42]. In addition, the women in this study had lower weight compared with peri- and postmenopausal Australian women in a previous study on uric acid and BMD [16]. Thus, the observed associations of uric acid with menopause and BMD were less likely to be confounded by obesity and other comorbidity, but the generalizability of the findings to other populations may be limited. In addition, BMD measurement was performed voluntarily, which could introduce selection bias. However, women in the analysis were comparable to those excluded from the analysis, most of whom had not had BMD measurement and excluded. Fourth, the observed association was marginally significant. We speculate that it is mostly likely due to relatively small sample size because the finding was consistent throughout various models. Lastly, any observational studies like this one cannot be free of possible confounding due to uncontrolled or unmeasured variables. Several important variables such as bone turnover markers, PTH, and serum 25-hydroxyvitamin D were not measured or available for the analysis.

Despite these limitations, the study has several strengths. Even though this was a retrospective analysis, the data were drawn from medical records for health checkup, which were in general free of missing values except for a few measurements. These measurements were performed voluntarily or as a part of optional examinations. The main finding was robust to the inclusion of a variety of covariates including years after menopause and exclusion of older women.

In conclusion, the present study showed that higher uric acid levels in the physiologic range of uric acid are linearly associated with higher lumbar spine bone mineral density in peri- and postmenopausal Japanese women. Further research is needed to elucidate the precise underlying mechanism of the association between uric acid and bone mineral density and to determine if the positive association between BMD and uric acid is still observed in the hyperuricemic range.

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Conflicts of interest None.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Association of decreased sympathetic nervous activity with mortality of older adults in long-term care

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Aim: To investigate the relationship between physical function, mortality and autonomic nervous activity measured by heart rate variability of elderly in long-term care.

Methods: Cross-sectional and longitudinal studies were carried out at hospitals and health service facilities for the elderly in Nagano prefecture, Japan, from July 2007 to March 2011. A total of 105 long-term care older adults and 17 control older adults with independent physical function were included. The Functional Independence Measure (FIM) and Barthel Index were determined as indices of physical function. Twenty-four-hour Holter monitoring was carried out. From RR intervals in electrocardiograms, heart rate and standard deviations of all NN intervals in all 5-min segments of the entire recording, power spectral density, low frequency, high frequency and low frequency/high frequency (LF/HF) were calculated.

Results: FIM score and Barthel Index were 46 ± 26 and 30 ± 31, respectively, in long-term care elderly. FIM and Barthel index were significantly correlated with heart rate and the standard deviations of all NN intervals after adjustment for age, sex, cardiovascular risk factors and FIM. Furthermore, LF/HF was significantly decreased in long-term care elderly compared with control elderly after adjustment for covariates. In addition, decrease in LF/HF was an independent risk factor for mortality.

Conclusion: Low LF/HF activity was observed in long-term care elderly and was related to an increase of overall mortality. **Geriatr Gerontol Int 2014; 14: 159–166.**

Keywords: heart rate variability, long-term care, mortality, motor activity, sympathetic nervous system.

Introduction

The number of older adults who require long-term care (LTC) has been increasing in Japan, and it was reported that there were 4.67 million older adults in LTC in 2008.[1] One of the characteristics of older adults in long-term care is physical and cognitive dysfunction. Physical dysfunction, including slow gait, low handgrip strength, low physical activity, weight loss and exhaustion, are reported to be associated with increased overall mortality.[2] In Japan, LTC elderly is defined as those who require assistance with walking, moving, and washing their face, body and mouth, representing functional disability and high mortality.[3] Thus, it is important to maintain or increase physical function in LTC elderly.

The underlying causes of physical dysfunction in Japanese LTC elderly include cerebrovascular disease, dementia, fractures, falls, weakness as a result of aging, and arthritis.[3] Recent studies have shown that these diseases with physical dysfunction are associated with low sympathetic nervous system activity.[4–7]

Skin sympathetic reactivity (SSR) reflects sympathetic nervous system activity. Muslumanoglu *et al.* showed that low SSR was associated with greater severity of paralysis, and depression of sympathetic reflex activity was associated with moderate or severely limited motor function in the chronic phase of ischemic cerebrovascular disease in elderly patients.[5] In addition, low plasma norepinephrine and low iodine-131-meta-iodobenzylguanidine (^{123}I-MIBG) uptake were observed in patients with Lewy body dementia compared with normal healthy subjects.[6,7] RR intervals in the electrocardiogram are utilized to evaluate heart rate variability

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(HRV), which reflects autonomic nervous system activity.[8] In practice, low frequency/high frequency (LF/HF), a marker of sympathovagal balance or sympathetic modulation, showed a positive correlation with respiratory and skeletal muscle strength in chronic obstructive pulmonary disease.[4] Furthermore, decreased LF/HF was related to overall mortality in frail older adults.[9]

In addition to measurement of SSR, norepinephrine spillover and ^{123}I-MIBG scintigraphy uptake, HRV has recently been used as a marker of autonomic nervous function.[8] HF was reported to reflect parasympathetic nervous system activity and LF/HF to represent sympathovagal balance or sympathetic modulation. In addition, decreased HRV was associated with cardiovascular disease (CVD),[10] cardiac death[11] and all-cause mortality.[9] Whereas HRV is known to decrease with the aging process,[12,13] little is known about the relationship between sympathetic nervous activity and mortality in LTC elderly.

In the Framingham heart study, a cohort study in American community-dwelling people, mortality and HRV were investigated in older adults, and it was not shown that low LF/HF correlated with mortality,[14] whereas in a cohort study of frail older adults, low LF/HF was significantly correlated with both frailty and mortality in the Women's Health and Aging Study-I (WHAS-I).[9]

Aging attenuates sympathetic nervous modulation,[12,13] and previous studies suggested that low sympathetic nervous activity might be associated with physical and cognitive dysfunction. However, only some of the subjects were frail or LTC elderly,[9,14] and there is little evidence describing the relationship between physical function, mortality and sympathetic nervous activity in LTC elderly. In particular, few studies have focused on the specific characteristics of sympathetic nervous activity in LTC elderly. Therefore, we investigated the relationship between sympathetic nervous activity, measured by HRV, and physical function and mortality in older adults in LTC.

Methods

Study design and participants

The present observational study analyzed 105 consecutive older adults in LTC aged 75 years or older who were admitted to a rehabilitation unit or a health service facility for older adults that provided rehabilitation. All hospitals and health service facilities were located in Nagano prefecture, Japan. Inclusion criteria were older adults in LTC aged 75 years or older receiving rehabilitation. Exclusion criteria were treatment of acute phase diseases within the past 2 weeks, arrhythmia, administration of anti-arrhythmia drugs or β-blockers, malignancy and neurodegenerative diseases other than dementia. As a control for the present study, we recruited 17 elderly outpatients with intact activities of daily living (ADL) who were matched for age, sex and CVD risk factors. The same inclusion and exclusion criteria were used for these control subjects. Medical records were reviewed to obtain information about the medical history of CVD, such as hypertension, diabetes mellitus, hyperlipidemia, chronic heart failure and ischemic heart disease, which was confirmed by the patients or their family. The present study protocol was approved by the institutional review board of the facility. Written informed consent was obtained from all participants or their families.

Heart rate variability

Ambulatory Holter recording was carried out for 24 h using QR2100 (Fukuda ME Kogyo, Tokyo, Japan) and processed with HS1000VL (Fukuda ME Kogyo). For time domain analysis, the standard deviations of all NN intervals in all 5-min segments of the entire recording (SDANN) were calculated, and frequent domain analysis was carried out with fast Fourier transform. From the power spectral density, low frequency (LF; 0.04~0.15 Hz), high frequency (HF; 0.15~0.40 Hz) and low frequency/high frequency (LF/HF) were determined.

Anthropometric, physical function and hematological measures

Height, weight and body mass index (BMI) were measured before Holter monitoring. The Functional Independence Measure (FIM)[15] and Barthel Index[16] were determined in order to assess physical function. Venous blood samples were obtained from participants in the morning after an overnight fast. Blood cell counts and serum levels of chemical parameters were determined by a commercial laboratory (Health Science Research Institute, Yokohama, Japan).

Statistical analysis

Data were analyzed using SPSS software version 11.0.1J (SPSS Japan, Tokyo, Japan). Mann–Whitney *U*-test for continuous variables and χ^2-test for categorical variables were used to compare controls and LTC elderly. Pearson's correlation coefficient was calculated, and standardized multiple regression analysis of HRV indices was carried out with age, sex, FIM, Barthel Index and blood nutritional data as covariates. Multiple regression analysis was used to calculate Cox hazard ratio, with adjustment for age, sex, clinical risk factors and FIM. Kaplan–Meier survival rate was computed for HRV indices.

Table 1 Characteristics of long-term care elderly and healthy elderly controls

	LTC elderly	Controls	*P*
No. participants	105	17	
Age (years)	86.5 ± 6.0 (75–100)	86.3 ± 9.1 (75–103)	0.311
Sex, male (%)	29 (27.6)	6 (35.3)	0.999
Body mass index	19.5 ± 3.3	22.0 ± 3.5	0.009
Cardiovascular risk factors, *n* (%)			
Hypertension	57 (54.3)	11 (64.7)	0.590
Diabetes mellitus	13 (12.4)	2 (11.8)	0.999
Hyperlipidemia	14 (13.3)	3 (17.6)	0.921
Chronic heart failure	12 (11.4)	1 (5.9)	0.792
Ischemic heart disease	15 (14.3)	1 (5.9)	0.572
Physical function			
FIM	46 ± 26	116 ± 24	<0.001
Barthel Index	30 ± 31	92 ± 16	<0.001
Blood nutritional data			
Albumin (g/dL)	3.5 ± 0.5	3.9 ± 0.3	<0.001
Hemoglobin (g/dL)	12.0 ± 1.8	12.4 ± 2.2	0.188
Total cholesterol (mg/dL)	177 ± 40	175 ± 34	0.892
Heart rate variability indices			
SDANN	85.0 ± 34.3	112.1 ± 27.2	0.001
Heart rate (b.p.m.)	73.1 ± 12.1	71.5 ± 7.4	0.878
LF (ms^2)	36.1 ± 25.3	42.4 ± 37.5	0.274
HF (ms^2)	65.9 ± 56.3	60.7 ± 52.3	0.813
LF/HF	0.69 ± 0.27†	0.87 ± 0.31	0.023

Values are mean ± standard deviation. †After adjusted for age, sex, cardiovascular risk factors and Function Independent Measure (FIM), low frequency/high frequency (LF/HF) were significantly lower in long-term care elderly than healthy controls ($P = 0.049$). HF, high frequency; LF, low frequency; SDANN, standard deviations of the all NN intervals in all 5-min segments of the entire recording.

Results

We registered 105 elderly in LTC, and assessed HRV from 24-h Holter monitoring. The underlying diseases of older adults in LTC for rehabilitation were cerebrovascular disease ($n = 59$, 56.2%), disuse syndrome ($n = 26$, 24.8%), fracture ($n = 19$, 18.1%) and dementia ($n = 1$, 1.0%). The proportions of underlying diseases were similar to those reported in Japanese older adults in LTC.[3]

The background data of the present study are shown in Table 1. In LTC elderly, mean age was 86.5 ± 6.0 years, blood nutritional data including albumin, hemoglobin and total cholesterol were at the lower limit of the normal range, and physical function represented by FIM and Barthel Index was significantly lower (46 ± 26 and 30 ± 31, respectively) than that in elderly controls (116 ± 24 and 92 ± 16, respectively). Scores for each FIM item were as follow: eating 3.7 ± 2.2, grooming 2.6 ± 1.8, bathing 1.5 ± 1.1, upper body dressing 2.5 ± 1.7, lower body dressing 2.2 ± 1.6, toileting 2.7 ± 2.0, bladder management 2.6 ± 2.1, bowel management 2.4 ± 2.0, bed to chair transfer 3.0 ± 1.9, toilet transfer 2.4 ± 1.7, shower transfer 1.5 ± 1.4, locomotion (ambulatory or wheelchair level) 2.0 ± 1.8, stairs 1.2 ± 0.8, cognitive comprehension 3.6 ± 2.2, expression 3.6 ± 2.2, social interaction 3.2 ± 2.2, problem solving 2.8 ± 1.9 and memory 2.8 ± 1.9. These score showed that the overall participants required moderate care supporting physical and cognitive function. In addition, BMI, albumin, SDANN and LF/HF were significantly decreased in LTC elderly compared with elderly controls. After adjustment for covariance, of all HRV indices, only LF/HF was significantly lower in LTC elderly (Table 1). Data of HRV indices were obtained every 5 min, and averaged every 3 h to examine the circadian rhythm in both LTC elderly and healthy controls. A significant decrease of LF/HF was observed in the night-time in healthy controls, whereas there was a loss of circadian rhythm in LTC elderly (Fig. 1).

Multiple regression analysis showed that the associations between heart rate, SDANN and physical function (Barthel Index and FIM) were independent of age, sex, and CVD. Furthermore, albumin and hemoglobin were also correlated with heart rate and SDANN. In contrast, LF, HF and LF/HF were not significantly correlated with physical function and blood nutritional data (Table 2).

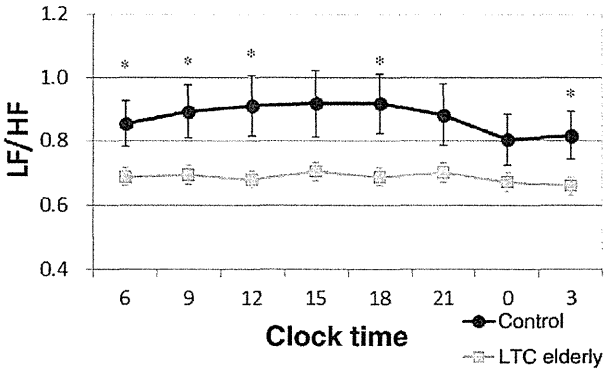

Figure 1 The activity of low frequency/high frequency (LF/HF) in long-term care (LTC) elderly and controls. The RR interval data were measured every 5 min, and averaged every 3 h. *$P < 0.05$, mean ± SEM,

Next, we followed the survival of LTC elderly, and 23 people died among 105 LTC elderly during a mean follow-up period of 8.9 months. The major cause of death was pneumonia ($n = 12$). There was no sign of stroke among the study participants, and one participant with acute myocardial infarction was observed during the follow-up period. Mortality according to HRV indices divided by the average is shown in Table 3. After adjustment for covariates, of all HRV indices, only LF/HF was associated with mortality. Kaplan–Meier survival curves also showed an association between decreased LF/HF and high mortality (Fig. 2). In addition to adjusted covariates, BMI, Barthel Index, and blood nutritional data were not different between the high LF/HF group and low LF/HF group (data not shown).

Discussion

In the present study, we investigated the relationship between physical function, mortality and sympathetic nervous activity measured by HRV in Japanese LTC elderly, and it was shown that LF/HF was significantly decreased in LTC elderly after adjustment for age, sex, CVD risk factors and FIM compared with elderly controls. In addition, the circadian rhythm of LF/HF was lost in LTC elderly, and low LF/HF was associated with overall mortality.

In a previous study, low LF/HF was associated with both frailty and mortality in community-dwelling people of whom one-third were frail elderly,[9] and these associations were consistent with the present data. Additionally, low LF/HF was also shown in LTC elderly, and was independent of physical function.

Elevated heart rate or low SDANN leads to cardiovascular disease and low physical function,[17,18] and the same relationship was also observed in LTC elderly. Furthermore, low albumin and low hemoglobin were observed in the high heart rate group, and limited physical function was observed in LTC elderly. These results are supported by a previous report.[19] So it might be possible to improve the physical function of LTC elderly by maintaining their nutritional state. The high LF/HF group has been reported to show high physical function and muscle mass,[4,20] whereas the present data did not show this association. One of the reasons for this discrepancy is thought to be the effect of aging. Aging generally attenuates LF/HF, and the patients in the present study were older than those in other studies.[9,14] Another reason might be autonomic nervous system disturbance. In particular, the circadian rhythm of LF/HF was impaired in LTC elderly.

Circadian imbalance of LF/HF has been shown in some disorders, such as Parkinson's disease, type 2 diabetes mellitus (T2DM) and ischemic stroke;[21–23] and furthermore, physical activity also influences HRV indices.[24,25] In the present study, LTC elderly with Parkinson's disease were excluded, and CVD risk factors including T2DM were matched between LTC elderly and healthy controls, as stroke and physical activity might affect LF/HF. However, the influence of both conditions on LF/HF is controversial. High physical activity and good posture led to high LF/HF activity,[26] whereas it was also suggested that LF/HF was not affected by physical activity.[13] The effect of LF/HF on stroke is also controversial.[23,27,28] In ischemic stroke patients, LF/HF was higher than healthy controls in some studies,[27,28] whereas another study suggested that LF/HF was lower in patients.[23] So the mechanism of LF/HF circadian rhythm disturbance is not clear, though its recovery might be important to increase physical function in LTC elderly. Other reasons why LF/HF and physical function did not show a correlation in LTC elderly might to be the effects of stroke, insufficient exposure to daylight and posture at daytime. All participants were aged over 75 years in the present study, and there is a possibility that asymptomatic lacunar infarction might be observed. It has also been suggested that lacunar infarction disturbs the autonomic nervous system, leading to a decrease in LF/HF and the related value of the autonomic nervous system, resulting in a disappearance of the correlation between physical activity and LF/HF. In addition, exposure to daylight was known to be one of the most powerful rhythmic regulators in the environment.[29] All participants in the present study spent their time indoors for rehabilitation and care. Furthermore, it is known that the supine position increases HF and decreases LF/HF,[30] and LTC elderly participants who were at rehabilitation units or health service facilities might spend more time in bed compared with outpatient controls, leading to low LF/HF and disappearance of the correlation between LF/HF and physical activity in the present study.

Table 2 Multiple regression analysis of heart rate variability indices with physical function and blood nutritional data after adjusted for age, sex and cardiovascular risk factors

	HR	SDANN	LF	HF	LF/HF
FIM	−0.25*	0.28*	0.19	0.15	−0.08
Barthel Index	−0.27*	0.29*	0.08	0.04	0.00
Body mass index	−0.05	0.05	0.00	−0.08	0.19
Albumin	−0.21*	0.25*	0.05	−0.02	0.11
Hemoglobin	−0.20*	0.27*	0.12	0.12	0.05
Total cholesterol	−0.01	−0.05	−0.13	−0.17	0.03

*$P < 0.05$, analyzed in 105 long-term care elderly. FIM, function independent measure; HF, high frequency; HR, heart rate; LF, low frequency; SDANN, standard deviations of the all NN intervals in all 5-min segments of the entire recording.

Table 3 Proportional hazards regression analysis of the impact of heart rate variability measure on overall mortality

	Hazard ratio†	95% Confidence interval	*P*
Unadjusted			
SDANN (ms)	1.84	0.77–4.38	0.171
LF (ms^2)	1.61	0.59–4.38	0.353
HF (ms^2)	2.14	0.72–6.34	0.169
LF/HF	4.73	1.59–14.06	0.005
Age, sex and cardiovascular risk factors adjusted for association with mortality			
SDANN (ms)	1.53	0.60–3.86	0.372
LF (ms^2)	1.65	0.57–4.78	0.357
HF (ms^2)	2.60	0.82–8.22	0.105
LF/HF	3.37	1.02–11.07	0.046
Age, sex, FIM and cardiovascular risk factors adjusted for association with mortality			
SDANN (ms)	1.19	0.44–3.17	0.736
LF (ms^2)	1.49	0.50–4.41	0.475
HF (ms^2)	2.85	0.83–9.83	0.097
LF/HF	3.61	1.08–12.10	0.038

Based on 23 deaths among 105 participants. Mean values of heart rate variability measure are in Table 1. †Hazard ratio of death rates of participants whose heart rate variability were less than average. FIM, function independent measure; HF, high frequency; HR, heart rate; LF, low frequency; SDANN, standard deviations of the all NN intervals in all 5-min segments of the entire recording.

Recent studies showed that decreased HRV indices including LF, HF and LF/HF were associated with CVD risk factors, and decreased LF was an independent predictor of death in elderly people.[31,32] However, the present findings showed that, of all HRV indices, only LF/HF was associated with mortality. This result is supported by a previous study in which, of HRV indices, LF/HF was associated with both frailty and mortality.[9] The major difference between the present study and other studies is whether or not the participants included frail LTC elderly. All participants were LTC elderly in the present study and WHAS-I, which was reported by Varadhan *et al.* and consisted of one-third frail elderly, whereas in other studies the participants were community-dwelling older adults with intact ADL, and they did not consider physical function.[14,32,33] These results suggest that the significance of LF/HF might differ between LTC elderly and elderly with intact ADL and physical function.

There is a discrepancy in the results derived from studies of LTC elderly and studies of elderly with intact physical function regarding sympathetic nervous activity. Exercise activates the sympathetic nervous system, leading to an increase in blood pressure, muscle blood

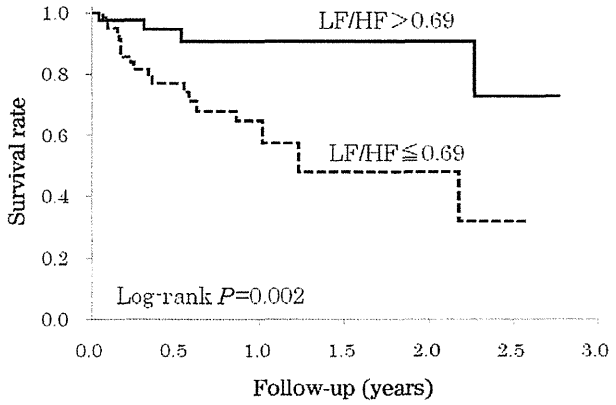

Figure 2 Kaplan–Meyer survival curves for death according to low frequency/high frequency (LF/HF). Mortality was significantly higher for patients with low LF/HF than for patients with high LF/HF. The mean follow-up period was 8.9 months.

flow and muscle strength by inducing muscle protein synthesis,[34–37] suggesting that low sympathetic nervous activity is related to not only physical dysfunction, but also the inability to maintain muscle strength, leading to a worse outcome in LTC elderly. Appropriate activation of the sympathetic nervous system might prevent muscle wasting and improve overall mortality in LTC elderly.

Activation of the sympathetic nervous system has been applied to aging or sarcopenic model rats. The β2-adrenergic agonists, clenbuterol and formoterol, improved muscle mass and muscle strength, and prevented muscle aging in aging, disuse and sarcopenia[38–44] model rats. In contrast, inhibition of sympathetic nervous activity with β-blockers was associated with a worse outcome in older adults.[45] These findings also suggest the importance of preventing a sympathetic nervous activity decline in LTC elderly.

There were several study limitations. First, this was an observational study, and could not provide direct evidence of causality. So it will be necessary to carry out randomized controlled trials to show whether high sympathetic nervous activity leads to a good outcome or not. Second, excessive sympathetic nervous activity is associated with cardiovascular risk factors, such as hypertension, left ventricular myocardial hypertrophy and old cerebrovascular disease.[46,47] In addition, the number of control subjects was relatively small in the present study. Based on these results, it might be hard to apply the findings in the present study to the oldest old population in general. However, some studies, particularly in the elderly, showed that decreased sympathetic nervous activity was associated with a worse outcome.[9] In addition to low physical activity, poor handgrip strength and frailty are known to be important risk factors predicting death older adults,[2,48–50] and few reports have focused on LTC elderly. Therefore, the present study has the possibility of providing evidence to improve physical function and mortality in LTC elderly by means of maintaining or increasing LF/HF.

In summary, the present study showed that LF/HF is a factor that distinguishes LTC elderly from elderly controls independent of physical function. In addition, the circadian rhythm of LF/HF was lost in LTC elderly. Furthermore, low LF/HF was associated with high mortality. For LTC elderly aged 75 years or over, LF/HF might be a predictive biomarker of physical function and mortality.

Disclosure statement

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