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ORIGINAL ARTICLE

Association between frailty and bone loss in patients undergoing maintenance hemodialysis

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Abstract
Frailty is significantly associated with bone loss in the general population. However, it is unclear whether this association also exists in patients undergoing hemodialysis who have chronic kidney disease-mineral and bone disorder (CKD-MBD). This study aimed to assess the association between frailty and bone loss in patients undergoing hemodialysis. This cross-sectional study included 214 (90 women, 124 men) Japanese outpatients undergoing maintenance hemodialysis three times per week, with a mean age of 67.1 years (women) and 66.8 years (men). Frailty was defined based on criteria set forth by the Cardiovascular Health Study (CHS)—19 (21.1%) women and 47 (37.9%) men were robust, 41 (45.6%) women and 43 (34.7%) men were pre-frail, and 30 (33.3%) women and 34 (27.4%) men were frail. For bone mass, quantitative ultrasound (QUS) parameters (speed of sound, broadband ultrasound attenuation, stiffness index) of the calcaneus were measured. The association between frailty and QUS parameters was determined separately for women and men using multivariate analysis of covariance (ANCOVA), with adjustments for clinical characteristics including age, body mass index, hemodialysis vintage, diabetes, current smoking, serum albumin, phosphate, corrected calcium, intact parathyroid hormone, and medication for CKD-MBD (vitamin D receptor activator, calcimimetics). ANCOVA revealed that all QUS parameters declined significantly with increasing levels of frailty in both sexes ($P < 0.05$). In conclusion, frailty (as defined by CHS criteria) should be considered a risk factor for bone loss in patients undergoing hemodialysis.

Keywords Frailty · Hemodialysis · QUS · Bone mass · CKD-MBD

Introduction

Fractures commonly occur in patients undergoing maintenance hemodialysis [1]. The incidence of hip fracture among Japanese patients undergoing hemodialysis is reportedly about five-fold higher than among the general population [1]. In addition, patients with stage 5 chronic kidney disease (CKD) with fractures have a two-fold increase in mortality compared to those without fractures [2]. The measurement of bone mass is an integral component of the assessment of bone strength and fracture risk [3]. Kidney failure accelerates bone loss via abnormal mineral metabolism and an elevation in levels of intact parathyroid hormone (iPTH). The disorder associated with adverse outcomes from this systemic condition in patients with CKD is referred to as CKD–mineral and bone disorder (MBD) [4, 5]. A previous systematic review reported that, in patients undergoing hemodialysis, those with fractures had significantly

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lower bone mass than those without fractures [6]. Given the increasing number of patients with end-stage renal disease (ESRD) who are being treated with renal replacement therapy worldwide [7, 8], a reduction in bone mass in this population is likely to exacerbate the problem.

In a study that used data from the US Renal Data System, the prevalence of frailty, an age-associated medical syndrome of decreased physiological reserve [9, 10], was found to be higher among patients with ESRD compared to community-dwelling populations [11]. Recent epidemiological studies in community-dwelling populations have also reported that frailty is linked with reduced bone mass [12, 13]. Although frailty may be an important factor related to reduced bone mass in patients undergoing hemodialysis, there is a lack of evidence of this in the literature. Assessing the association between frailty and bone loss in this patient population could contribute to better risk management for bone loss in frail people, as well as in patients with CKD-MBD. To this end, the present study aimed to assess the association between frailty and bone loss in patients undergoing hemodialysis.

Materials and methods

Study population

This study was approved by the Ethics Committee of Kitasato University School of Allied Health Sciences. Informed consent was obtained from all individual participants included in the study. This study was conducted in accordance with the standards set forth in the latest revision of the Declaration of Helsinki.

Between September 2009 and July 2015, there were 420 Japanese outpatients undergoing maintenance hemodialysis three times per week at the Hemodialysis Center at Sagami Circulatory Organ Clinic. Subjects of this cross-sectional study were recruited from among these patients. Exclusion criteria were duration of maintenance hemodialysis <3 months, hospitalization <3 months prior to study enrollment, premenopausal women, undergoing treatment for osteoporosis, requirement for walking assistance, and other conditions that limited walking (e.g., dementia, low vision or blindness, paralysis due to stroke, leg amputation).

Clinical characteristics

Information regarding age, sex, height, weight, body mass index (BMI), hemodialysis vintage, primary cause of ESRD, comorbid conditions (diabetes), smoking history, serum albumin, phosphorus (P), calcium (Ca), iPTH, use of phosphate binders (calcium carbonate, lanthanum carbonate hydrate, and sevelamer hydrochloride), use of vitamin D receptor activators (alfacalcidol and calcitriol), and use of calcimimetics (cinacalcet hydrochloride) was obtained from clinical records. BMI was calculated by dividing weight in kilograms by the square of height in meters. Serum albumin, P, Ca, and iPTH levels were measured immediately before each hemodialysis session. To avoid underestimating hypercalcemia in patients with low albumin levels, when albumin levels were <4.0 g/dL, serum Ca levels were corrected for albumin levels by the modified Payne method, which is used in Japan as set forth by the Japanese Society for Dialysis Therapy; corrected Ca was calculated as Ca + (4.0 − albumin) [14].

Frailty

The 'gold standard' frailty criteria developed by Fried et al. [9] in the Cardiovascular Health Study (CHS) were used in this study. The criteria consisted of the following five components—weakness, exhaustion, weight loss, slowness, and low physical activity.

Weakness was determined based on the measurement of grip strength using a hand-held dynamometer (Grip-D; Takei Scientific Instruments, Niigata, Japan) according to modified cut-offs (women <18.0 kg, men <26.0 kg) for Japanese people [15, 16]. Exhaustion was determined by self-report using the Center for Epidemiologic Studies Depression (CES-D) scale [17]. Weight loss was determined according to CHS criteria. Slowness was determined by measuring walking speed at the usual pace along a 10-meter walk, a commonly used measure in Japan, rather than the 15-ft walk described by Fried et al. [9]. Slowness was determined according to the modified cut-off time of <1.0 m/s for Japanese people [16, 18]. Physical activity was measured in kilocalories per week using an accelerometer (Lifecorder; Suzuken Co. Ltd., Nagoya, Japan), and the same cut-off for low activity (women <270 kcal/week, men <383 kcal/week) described by Fried et al. [9] was used. Patients who met three or more of these criteria were characterized as frail, those who met one or two of the criteria were characterized as pre-frail, and those who met none of the criteria were characterized as robust.

Quantitative ultrasound calcaneal measurements

For bone mass, the following quantitative ultrasound (QUS) parameters of the calcaneus were measured: speed of sound (SOS, m/s), broadband ultrasound attenuation (BUA, dB/MHz), and the stiffness index [a parameter automatically derived from SOS and BUA (0.67 × BUA + 0.28 × SOS-420)]. SOS and BUA were measured using an Ultrasound Bone Densitometer (A-1000; GE-Healthcare Corporation, Madison, WI, USA) at the right calcaneus according to manufacturer's instructions. In our sub-study, in vivo precision

of the QUS device was 0.4% for SOS, 2.0% for BUA, and 1.7% for stiffness index based on six measurements on different days in 20 hemodialysis patients (10 women).

According to a previous study that used the same device as that used in the present study, stiffness index was highly and significantly correlated with lumbar spine, femoral neck, and total body bone mineral density (BMD) measured by dual X-ray absorptiometry (DXA) ($r = 0.80$, 0.77, and 0.78, respectively) [19]. Moreover, a systematic review [20] examined the usefulness of calcaneal QUS as a prescreen tool and concluded that this technique was potentially useful for assessing osteoporosis. In addition, QUS parameters have been shown to be closely correlated with BMD (as determined by DXA: SOS, $r = 0.84$; BUA, $r = 0.72$: stiffness index, $r = 0.83$) among not only the general population, but patients undergoing hemodialysis as well [21].

Statistical analysis

Given the considerable sex-based differences in bone metabolism among our subjects, data for women and men were analyzed separately. The Statistical Package for the Social Sciences 22.0 (IBM Corp, Armonk, NY, USA) was used for statistical analyses. $P < 0.05$ was considered statistically significant.

Differences in clinical characteristics and QUS parameters by frailty status were tested for significance by analysis of variance (ANOVA) or the chi-squared test. Analysis of covariance (ANCOVA) was used to assess independent associations between frailty status and QUS parameters, after adjusting for clinical characteristics including age, BMI, hemodialysis vintage, diabetes, current smoking, albumin, P, corrected Ca, iPTH, use of vitamin D receptor activators, and use of calcimimetics. Based on ANCOVA, estimated marginal mean values (95% CI) of QUS parameters for each frailty category were calculated to represent changes in QUS parameters for each increase in level of frailty.

To identify which criteria of frailty were more closely related to QUS parameters in each sex, we analyzed associations between individual frailty criteria and QUS parameters using multivariate linear analysis adjusted for age, BMI, hemodialysis vintage, diabetes, current smoking, albumin, P, corrected Ca, iPTH, use of vitamin D receptor activators, and use of calcimimetics. In these analyses, standardized beta coefficients indicated the impact of individual frailty criteria on QUS parameters.

Results

Differences in clinical characteristics by frailty status

In this population survey, 56 of 420 Japanese outpatients undergoing hemodialysis who were assessed for eligibility fell under the exclusion criteria, and 150 declined to participate (Fig. 1). Consequently, data from 214 subjects (90 women, 124 men) were analyzed.

Table 1 shows differences in clinical characteristics of women (mean age, 67.1 years; age range, 50–89 years) by frailty status. According to CHS criteria, 19 (21.1%) subjects were robust, 41 (45.6%) were pre-frail, and 30 (33.3%) were frail. ANOVA and chi-squared tests revealed that age, corrected Ca, and frailty components (with the exception of weight loss) significantly differed by frailty status.

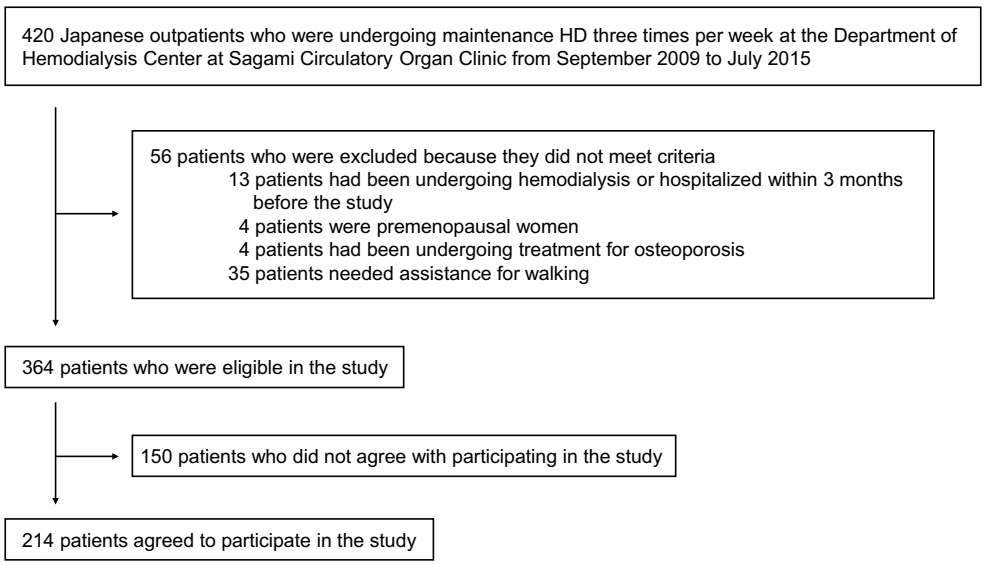

Fig. 1 Flow diagram of the participant selection and exclusion process

Table 1 Differences in clinical characteristics by frailty status (according to Cardiovascular Health Study criteria) in female patients undergoing hemodialysis

Variables	Robust ($N = 19$)	Pre-frail ($N = 41$)	Frail ($N = 30$)	P value
Age (years)	63.0 ± 7.8	66.6 ± 5.8	70.5 ± 8.2	0.002
Body mass index (kg/m^2)	22.2 ± 4.1	20.3 ± 3.8	20.2 ± 3.1	0.273
Hemodialysis vintage (months)	124.7 ± 87.1	163.9 ± 126.0	152.5 ± 140.6	0.528
Cause of end-stage renal disease (%)				0.534
Glomerulonephritis	8 (42.1)	20 (48.8)	7 (23.3)	
Diabetes	5 (26.3)	7 (17.1)	11 (36.7)	
Hypertension	0 (0.0)	1 (2.4)	1 (3.3)	
Unknown	3 (15.8)	5 (12.2)	4 (13.3)	
Others	3 (15.8)	8 (19.5)	7 (23.3)	
Comorbidities (%)				0.628
Diabetes	6 (31.6)	12 (29.3)	12 (40.0)	
Smoking history (%)				0.995
Never	10 (52.6)	20 (48.8)	15 (50.0)	
Past	6 (31.6)	15 (36.6)	11 (36.7)	
Current	3 (15.8)	6 (14.6)	4 (13.3)	
Laboratory parameters				
Albumin (g/dL)	3.9 ± 0.3	3.8 ± 0.4	3.8 ± 0.2	0.273
Phosphorus (mg/dL)	5.1 ± 0.9	5.0 ± 0.9	5.0 ± 0.9	0.889
Corrected Ca[a] (mg/dL)	9.0 ± 0.4	9.4 ± 0.5	9.3 ± 0.5	0.018
Intact PTH (pg/mL)	124.6 ± 115.0	132.9 ± 125.9	152.8 ± 126.0	0.697
Medication (%)				
Vitamin D receptor activator				
Alfacalcidol	9 (47.4)	17 (41.5)	12 (40.0)	0.871
Calcitriol	1 (5.3)	5 (12.2)	4 (13.3)	0.652
Phosphate binder				
Calcium carbonate	17 (89.5)	36 (87.8)	22 (73.3)	0.195
Lanthanum carbonate hydrate	4 (21.1)	11 (26.8)	7 (23.3)	0.876
Sevelamer hydrochloride	7 (36.8)	9 (22.0)	7 (23.3)	0.443
Calcimimetic				
Cinacalcet hydrochloride	3 (15.8)	9 (22.0)	7 (23.3)	0.807
Components of frailty definition				
Weakness (%)	0 (0.0)	25 (61.0)	26 (86.7)	< 0.001
Grip strength (kg)	21.6 ± 2.9	18.1 ± 4.5	13.1 ± 3.6	< 0.001
Low physical activity (%)	0 (0.0)	9 (22.0)	25 (83.3)	< 0.001
Physical activity (kcal/week)	670.9 ± 436.2	483.0 ± 259.1	159.6 ± 139.1	< 0.001
Exhaustion (%)	0 (0.0)	12 (29.3)	22 (73.3)	< 0.001
Slowness (%)	0 (0.0)	8 (19.5)	25 (83.3)	< 0.001
Gait speed (m/s)	1.35 ± 0.16	1.17 ± 0.20	0.75 ± 0.29	< 0.001
Weight loss (%)	0 (0.0)	2 (4.9)	5 (16.7)	0.068

Values for categorical variables are expressed as number and percentages. Values for continuous variables are expressed as mean ± standard deviation. Differences were evaluated by analysis of variance for continuous variables and by chi-squared test for categorical variables

Ca calcium, *PTH* parathyroid hormone

[a]Albumin-corrected value: calcium + [4.0 − albumin], if albumin <4.0 g/dL

Table 2 shows differences in clinical characteristics of men (mean age 66.8 years; age range 34–89 years) by frailty status. According to CHS criteria, 47 (37.9%) subjects were robust, 43 (34.7%) were pre-frail, and 34 (27.4%) were frail.

Table 2 Differences in clinical characteristics by frailty status (according to Cardiovascular Health Study criteria) in male patients undergoing hemodialysis

Variables	Robust ($N = 47$)	Pre-frail ($N = 43$)	Frail ($N = 34$)	P value
Age (years)	61.5 ± 11.1	68.6 ± 10.4	71.7 ± 9.0	< 0.001
Body mass index (kg/m^2)	22.1 ± 3.0	21.5 ± 3.0	20.9 ± 3.4	0.216
Hemodialysis vintage (months)	108.7 ± 90.3	97.2 ± 88.8	90.5 ± 108.2	0.681
Cause of end-stage renal disease (%)				0.733
Glomerulonephritis	14 (29.8)	13 (30.2)	6 (17.6)	
Diabetes	17 (36.2)	12 (27.9)	16 (47.1)	
Hypertension	0 (0.0)	1 (2.3)	1 (2.9)	
Unknown	7 (14.9)	8 (18.6)	4 (11.8)	
Others	9 (19.1)	9 (20.9)	7 (20.6)	
Comorbidities (%)				0.151
Diabetes	20 (42.6)	18 (41.9)	21 (61.8)	
Smoking history (%)				0.790
Never	21 (44.7)	14 (32.6)	12 (35.3)	
Past	19 (40.4)	21 (48.8)	15 (44.1)	
Current	7 (14.9)	8 (18.6)	7 (20.6)	
Laboratory parameters				
Albumin (g/dL)	3.9 ± 0.3	3.9 ± 0.2	3.7 ± 0.3	0.001
Phosphorus (mg/dL)	5.1 ± 1.0	5.2 ± 1.0	5.2 ± 1.0	0.940
Corrected Ca[a] (mg/dL)	9.1 ± 0.6	9.1 ± 0.5	9.3 ± 0.5	0.358
Intact PTH (pg/mL)	132.2 ± 97.6	140.7 ± 129.4	101.7 ± 80.4	0.258
Medication (%)				
Vitamin D receptor activator				
Alfacalcidol	22 (46.8)	19 (44.2)	21 (61.8)	0.265
Calcitriol	6 (12.8)	7 (16.3)	2 (5.9)	0.375
Phosphate binder				
Calcium carbonate	40 (85.1)	38 (88.4)	28 (82.4)	0.755
Lanthanum carbonate hydrate	15 (31.9)	11 (25.6)	5 (14.7)	0.209
Sevelamer hydrochloride	10 (21.3)	7 (16.3)	3 (8.8)	0.323
Calcimimetic				
Cinacalcet hydrochloride	11 (23.4)	10 (23.3)	5 (14.7)	0.574
Components of frailty definition				
Weakness (%)	0 (0.0)	19 (44.2)	30 (88.2)	< 0.001
Grip strength (kg)	33.4 ± 5.0	27.7 ± 67.1	21.4 ± 4.4	< 0.001
Low physical activity (%)	0 (0.0)	24 (55.8)	28 (82.4)	< 0.001
Physical activity (kcal/week)	1140.0 ± 798.8	501.3 ± 442.9	216.4 ± 157.6	< 0.001
Exhaustion (%)	0 (0.0)	13 (30.2)	20 (58.8)	< 0.001
Slowness (%)	0 (0.0)	5 (11.6)	25 (73.5)	< 0.001
Gait speed (m/s)	1.37 ± 0.18	1.23 ± 0.23	0.90 ± 0.25	< 0.001
Weight loss (%)	0 (0.0)	3 (7.0)	6 (17.6)	0.010

Values for categorical variables are expressed as percentages. Values for continuous variables are expressed as mean ± standard deviation. Differences were evaluated by analysis of variance for continuous variables and by chi-squared test for categorical variables

Ca calcium, *PTH* parathyroid hormone

[a]Albumin-corrected value: calcium + [4.0 − albumin], if albumin <4.0 g/dL

ANOVA and chi-squared tests revealed that age, albumin, and all frailty components significantly differed by frailty status.

Association between frailty and QUS parameters in women

As shown in Table 3, being frail, and even pre-frail, was associated with reduced SOS, BUA, and stiffness index in

Table 3 Marginal mean values (95% CI) of QUS parameters by frailty status (according to the Cardiovascular Health Study criteria) in female patients undergoing hemodialysis

Variables	Robust ($N = 19$)	Pre-frail ($N = 41$)	Frail ($N = 30$)
SOS (m/s)			
Unadjusted (95% CI)	1538.3 (1527.6, 1549.0)	1516.8 (1509.5, 1524.0)†	1488.0 (1479.5, 1496.6)†,‡
Model 1 (95% CI)	1537.3 (1526.0, 1548.5)	1517.5 (1510.3, 1524.7)†	1487.7 (1478.9, 1496.5)†,‡
Model 2 (95% CI)	1537.8 (1526.1, 1549.5)	1517.2 (1510.0, 1524.3)†	1487.8 (1479.1, 1496.5)†,‡
BUA (dB/MHz)			
Unadjusted (95% CI)	102.1 (98.1, 106.2)	91.6 (88.8, 94.3)†	85.3 (82.0, 88.5)†,‡
Model 1 (95% CI)	100.0 (95.9, 104.1)	91.6 (88.9, 94.2)†	86.6 (83.4, 89.8)†,‡
Model 2 (95% CI)	100.7 (96.3, 105.2)	91.5 (88.8, 94.2)†	86.2 (82.9, 89.5)†,‡
Stiffness index			
Unadjusted (95% CI)	78.8 (74.4, 83.3)	65.8 (62.7, 68.8)†	53.5 (50.0, 57.1)†,‡
Model 1 (95% CI)	77.1 (72.5, 81.7)	66.0 (63.0, 69.0)†	54.3 (50.7, 57.9)†,‡
Model 2 (95% CI)	77.7 (72.8, 82.6)	65.9 (62.9, 68.9)†	54.0 (50.4, 57.7)†,‡

Analyses were performed using analysis of covariance. Model 1 included age, body mass index, and current smoking. Model 2 additionally included hemodialysis vintage, diabetes, albumin, phosphorous, corrected calcium, intact parathyroid hormone, use of vitamin D, and use of cinacalcet

CI confidence interval, *SOS* speed of sound, *BUA* broadband ultrasound attenuation

†Statistically different from robust ($P < 0.05$)

‡Statistically different from pre-frail ($P < 0.05$)

women, after adjustment for age, BMI, hemodialysis vintage, diabetes, current smoking, albumin, P, corrected Ca, iPTH, use of vitamin D receptor activators, and use of calcimimetics (ANCOVA, $P < 0.05$ for all). Notably, all QUS parameters declined significantly with increasing levels of frailty.

When comparing the impact on QUS parameters across individual frailty criteria in women, low physical activity and slowness were more closely related to QUS parameters than other criteria in multivariate analysis adjusted for age, BMI, hemodialysis vintage, diabetes, current smoking, albumin, P, corrected Ca, iPTH, use of vitamin D receptor activators, and use of calcimimetics (Table 5).

Table 4 Marginal mean values (95% CI) of QUS parameters by frailty status (according to the Cardiovascular Health Study criteria) in male patients undergoing hemodialysis

Variables	Robust ($N = 47$)	Pre-frail ($N = 43$)	Frail ($N = 34$)
SOS (m/s)			
Unadjusted (95% CI)	1538.7 (1529.9, 1547.4)	1514.2 (1505.1, 1523.4)†	1497.2 (1486.9, 1507.5)†,‡
Model 1 (95% CI)	1541.4 (1532.2, 1550.5)	1513.3 (1504.2, 1522.5)†	1494.6 (1484.0, 1505.2)†,‡
Model 2 (95% CI)	1542.2 (1532.9, 1551.5)	1513.1 (1503.9, 1522.4)†	1493.7 (1482.5, 1504.9)†,‡
BUA (dB/MHz)			
Unadjusted (95% CI)	107.2 (103.8, 110.5)	101.4 (97.9, 104.9)†	94.1 (90.2, 98.1)†,‡
Model 1 (95% CI)	107.5 (104.1, 110.9)	101.2 (97.8, 104.6)†	93.9 (90.0, 97.9)†,‡
Model 2 (95% CI)	107.8 (104.6, 111.0)	101.1 (97.9, 104.3)†	93.8 (89.9, 97.6)†,‡
Stiffness index			
Unadjusted (95% CI)	82.3 (78.6, 85.9)	71.6 (67.8, 75.5)†	62.1 (57.7, 66.4)†,‡
Model 1 (95% CI)	83.2 (79.3, 87.0)	71.3 (67.4, 75.1)†	61.2 (56.8, 65.7)†,‡
Model 2 (95% CI)	83.6 (79.9, 87.3)	71.1 (67.4, 74.8)†	60.9 (56.4, 65.3)†,‡

Analyses were performed using analysis of covariance. Model 1 included age, body mass index, and current smoking. Model 2 additionally included hemodialysis vintage, diabetes, albumin, phosphorous, corrected calcium, intact parathyroid hormone, use of vitamin D, and use of cinacalcet

CI confidence interval, *SOS* speed of sound, *BUA* broadband ultrasound attenuation

†Statistically different from robust ($P < 0.05$)

‡Statistically different from pre-frail ($P < 0.05$)

Table 5 Differences in the impact of individual frailty criteria on QUS parameters in female patients undergoing hemodialysis

Variables	SOS		BUA		Stiffness index	
	Standardized β	P value	Standardized β	P value	Standardized β	P value
Frailty criteria (yes vs no)						
Weakness	− 0.253	0.034	− 0.209	0.068	− 0.271	0.018
Low physical activity	− 0.434	< 0.001	− 0.354	0.001	− 0.461	< 0.001
Exhaustion	− 0.332	0.002	− 0.210	0.045	− 0.323	0.002
Slowness	− 0.439	< 0.001	− 0.337	0.001	− 0.460	< 0.001
Weight loss	− 0.259	0.016	0.067	0.526	− 0.123	0.246

Analyses were performed using multivariate linear regression analysis adjusted for age, body mass index, hemodialysis vintage, current smoking, diabetes, albumin, phosphorous, corrected calcium, intact parathyroid hormone, use of vitamin D, and use of cinacalcet

SOS speed of sound, *BUA* broadband ultrasound attenuation

Association between frailty and QUS parameters in men

As shown in Table 4, being frail, and even pre-frail, was associated with reduced SOS, BUA, and stiffness index in men, after adjustment for age, BMI, hemodialysis vintage, diabetes, current smoking, albumin, P, corrected Ca, iPTH, use of vitamin D receptor activators, and use of calcimimetics (ANCOVA, $P < 0.05$ for all). Notably, all QUS parameters declined significantly with increasing levels of frailty.

When comparing the impact on QUS parameters across individual frailty criteria in men, low physical activity was more closely related to QUS parameters than other criteria in multivariate analysis adjusted for age, BMI, hemodialysis vintage, diabetes, current smoking, albumin, P, corrected Ca, iPTH, use of vitamin D receptor activators, and use of calcimimetics (Table 6).

Discussion

In this cross-sectional study of patients undergoing hemodialysis, frailty (according to CHS criteria) was significantly associated with calcaneal QUS parameters, including low SOS, BUA, and stiffness index for both sexes, even after adjusting for clinical characteristics. Interestingly, all QUS parameters declined significantly with increasing levels of frailty for both sexes. These findings suggest that identification of frailty in patients undergoing hemodialysis could allow for better risk management of bone loss in this patient population.

Previous studies targeting patients with CKD used slightly different criteria for frailty than that used in the present study. We applied the 'gold standard frailty criteria developed by Fried et al. [9]. As a result, the proportion of subjects who were robust was 31%, pre-frail was 39%, and frail was 30%. These percentages represent a larger number of individuals identified as frail than what had previously been derived using the CHS criteria in a previous Japanese epidemiological study [18]. Our results are consistent with the current understanding that the proportion

Table 6 Differences in the impact of individual frailty criteria on QUS parameters in male patients undergoing hemodialysis

Variables	SOS		BUA		Stiffness index	
	Standardized β	P value	Standardized β	P value	Standardized β	P value
Frailty criteria (yes vs no)						
Weakness	− 0.347	< 0.001	− 0.317	< 0.001	− 0.395	< 0.001
Low physical activity	− 0.402	< 0.001	− 0.371	< 0.001	− 0.461	< 0.001
Exhaustion	− 0.277	0.003	− 0.171	0.045	− 0.272	0.002
Slowness	− 0.305	0.002	− 0.299	0.001	− 0.360	< 0.001
Weight loss	− 0.186	0.056	− 0.117	0.184	− 0.183	0.048

Analyses were performed using multivariate linear regression analysis adjusted for age, body mass index, hemodialysis vintage, current smoking, diabetes, albumin, phosphorous, corrected calcium, intact parathyroid hormone, use of vitamin D, and use of cinacalcet

SOS speed of sound, *BUA* broadband ultrasound attenuation

of frail individuals is higher among hemodialysis patients than among community-dwelling people. A recent study of patients undergoing hemodialysis reported that the number of frail individuals who met the CHS criteria was 32% [22], which is consistent with our finding. The fact that the present findings are in agreement with previous reports supports our observations.

Risk factors associated with low bone mass (e.g., female sex, increased age, estrogen deficiency due to menopause, low weight or BMI, and smoking) are supported by evidence from large prospective studies. Moreover, patients undergoing hemodialysis acquire several disorders that affect bone health, such as CKD-MBD [23, 24]. Therefore, we fitted these covariates of risk factors for bone loss in the ANCOVA. In addition, given the considerable sex-dependent differences in bone metabolism of our subjects, data for women and men were analyzed separately. Similarly, given considerable differences in bone metabolism due to reduction in estrogen levels, premenopausal women were excluded from analysis. As a result, we found a significant association between frailty defined according to CHS criteria and calcaneal QUS parameters, including low SOS, BUA, and stiffness index in both sexes. To our knowledge, no study has assessed the association between frailty and QUS parameters in patients undergoing hemodialysis. Our findings are consistent with those reported in general population surveys. For instance, a previous cross-sectional study of a general population reported an association between frailty defined according to CHS criteria and decreased QUS parameters and femoral neck BMD [12]. One reason why our findings are similar to those of the general population could be that the patients in our study were treated for CKD-MBD and considered to have stable disease (i.e., mineral metabolism within target range) according to Japanese guidelines [25] (Tables 1, 2).

Each frailty criterion (i.e., weakness, low physical activity, exhaustion, slowness, and weight loss) could have a differential impact on bone mass. We thus compared the impact of individual frailty criteria on QUS parameters in each sex. As a result, we found that low physical activity and slowness in women, and low physical activity in men, were more closely related to QUS parameters (Tables 5, 6). In particular, sedentary lifestyle, which includes low physical activity, is a well-known modifiable risk factor associated with poor bone health [26]. Although this study is an observational study, these findings could provide useful data for the planning of effective therapeutic regimens in hemodialysis patients in future studies.

This study has several limitations. First, given the cross-sectional design of this study, causal associations between frailty and bone loss could not be determined. However, a previous longitudinal study reported that frailty at baseline predicted lower total hip and lumbar spine BMD one year later [13]. Thus, frailty could potentially cause bone loss, but further longitudinal studies will be needed to address this aspect. Second, since our subjects represented only a small fraction of patients undergoing hemodialysis in Japan, caution should be exercised when applying our findings to patients with different circumstances, e.g., those with uncontrolled mineral metabolism. Third, we could not account for all potential confounding factors when assessing the association between frailty and bone loss. For example, the normal aging process, which includes decreased estrogen levels due to menopause, is closely related to bone loss via bone remodeling [27], as well as to frailty via decreasing muscle mass and strength [28]. Due to the lack of sufficient data, further studies are still needed to identify the effect of additional confounding factors (e.g., estrogen levels, duration of menopause, and biochemical markers of bone metabolism) on bone mass. Finally, although DXA is considered the gold standard of bone strength measurement, we evaluated calcaneal QUS parameters. Using the same device as that used in our study, Thompson et al. [29] reported the following odds ratios per 1 SD decline in QUS parameters adjusted for age—SOS = 1.5, BUA = 1.6, and stiffness index = 1.8 for wrist fractures; and SOS = 1.6, BUA = 1.9, and stiffness index = 2.2 for osteoporosis-related fractures (hip, vertebra, pelvis, and humerus combined). However, there is no consensus on how to link the results of QUS to BMD measured by DXA at different sites (e.g., lumber spine). Although QUS parameters are easy and non-invasive to obtain and do not require radiation, a future study will be needed to evaluate BMD by DXA to verify our results.

In conclusion, 30% of our subjects met the CHS criteria for frailty. QUS parameters declined significantly with increasing levels of frailty, even after adjusting for common risk factors of bone loss and CKD-MBD markers. Our findings suggest that clinicians should consider frailty as a risk factor for bone loss.

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Compliance with ethical standards

Conflict of interest All authors have no conflict of interest to declare.

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