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Lower baseline value and greater decline in BMD as independent risk factors for mortality in community dwelling elderly☆

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ABSTRACT

Skeleton plays diverse roles via crosstalk between others, thus it is conceivable that lower BMD per se may reflect negative influences on health status and threats to life independent of fracture events. We investigated investigate the association between BMD and mortality, and to examine whether the rate of bone loss can predict future mortality in an elderly population. This study was conducted as a part of the Korean Longitudinal Study on Health and Aging, a community-based prospective study of Korean people aged 65 years and older that began in 2005. A total of 648 people (318 men and 330 women) were included. Dual energy X-ray absorptiometry were conducted at baseline and at 5 years. Mortality data were collected until the date of death or the last follow-up in December 2014. Osteoporosis in all skeletal sites significantly related to increased risk of mortality in men and women, but the associations were stronger for BMD in the femur neck and total hip than in the lumbar spine. A multivariable Cox proportional-hazards model showed that baseline BMD level was a significant independent predictor of increased all-cause mortality for all three skeletal sites in men, and for lumbar spine and total hip in women. Furthermore, faster bone loss of BMDs, as shown by the decline in BMD in the lumbar spine, femur neck, and total hip, was significantly related to increased risk of mortality after adjusting for all covariates in men. Faster BMD loss at femur neck was also related to the increased risks of mortality in women. Conclusively, both a lower baseline values and greater decline in BMD were associated with excess morality in community-dwelling elderly population; there associations were stronger in men than in women. This study emphasizes the importance of skeletal health for healthy aging, revealing lower bone mass and faster bone loss may be markers of poorer health that are driving excess mortality.

1. Introduction

Society is rapidly aging, and the increasing proportion of elderly people in the total population imposes socioeconomic and medical burdens [1]. Most human organs and tissues are influenced by the aging process to some degree. Some organs are more vulnerable to the aging process, whereas others are relatively resistant. Bone is a representative organ that changes markedly with aging [2]. Bone mass declines during aging, and accelerated loss of bone leads to low bone mass and eventually to osteoporosis [3]. A significant amount of bone loss that exceeds a certain threshold can cause failure in resistance to loading and, possibly to osteoporotic fractures [3,4]. Therefore, skeletal health status is an important factor related to health in elderly people life.

Osteoporotic fractures, especially hip and vertebral fractures, are linked to many adverse health outcomes including severe pain, limitation of movement, impairment of the ability to live an independent life, and poor quality of life [5,6]. The changes that happen after a fracture can make elderly people prone to infection and frailty, which can increase the risk of death [6].

Adequacy of bone mass is evaluated by measuring bone mineral density (BMD) using dual energy x-ray absorptiometry (DXA) and the T-score indicates relative bone mass compared to healthy young adults [7]. The skeleton plays diverse roles via crosstalk between organs about various functions such as energy metabolism and maintenance of lean

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mass [8,9]. Therefore, it is conceivable that low baseline BMD or rapid loss of BMD may indicate negative influences on health status beyond the potential for fracture events.

Previous epidemiologic studies have reported the significant associations between osteoporotic fractures and mortality in the elderly population [10,11]. However, the relationships between mortality and BMD values per se and between changes in BMD and mortality have not been evaluated thoroughly. In this study, we investigated the associations between site-specific BMD (lumbar spine, femoral neck, and total hip) and mortality in a population-based, prospective study of a community dwelling elderly cohort. We also examined whether the bone loss rate can predict future mortality.

2. Materials and methods

2.1. Study participants

This study was conducted as a part of the Korean Longitudinal Study on Health and Aging (KLoSHA), which was designed as a community-based prospective study on health, aging, and common geriatric diseases in Korean people aged 65 years and older, and has been previously described in detail [12]. For this study, study participants were selected using age- and gender-stratified random sampling from a roster of people aged 65 years and older. Baseline evaluations were performed from 2005 to 2006, and 1000 participants (439 men and 561 women) were initially enrolled at Seoul National University Bundang Hospital (SNUBH), Korea. DXA was performed as an ancillary study of bone and body composition. This study evaluated the DXA results for 648 (318 men and 330 women) of the 1000 participants.

The Institutional Review Board of SNUBH (B-0706/046-012, B-1304/198-109) approved the study protocol. Participants or their legal guardians were fully informed about study participation and gave informed consent.

2.2. Measurement of anthropometric parameters, biochemical parameters, and comorbidity

Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, with the participant in light clothing and without shoes. Blood pressures were measured using a standard procedure. For biochemical analyses, blood samples were collected after an overnight fast for at least 8 h. Serum glucose concentration was measured using the glucose-oxidase method (YSI 2300 STAT Glucose Analyzer; YSI Inc., Yellow Springs, OH, USA). Total cholesterol, creatinine, aspartate transaminase (AST), and alanine transaminase (ALT) concentrations were measured enzymatically (Hitachi 747, Hitachi Ltd., Tokyo, Japan). At the baseline visit, a detailed medical history, including any details of diabetes mellitus, hypertension, osteoporosis, and medications was recorded.

2.3. Bone mineral density and body composition measurements

BMD was measured in the lumbar spine, femoral neck, and total hip area using DXA (Lunar Prodigy; GE, Madison, WI, USA). Whole body composition was also measured using same instrument. All participants were given a light gown and pants to wear for this assessment. All DXA measurements were performed using the same machine and a standardized protocol and quality control was performed regularly by a phantom subject to ensure the reliability of the densitometry measurement. The coefficients of variation for DXA measurements for both BMD and body composition in our institute are < 2% for all measures. T-scores were calculated using reference ranges for Asian populations provided by the manufacturer. Low bone mass was defined as a BMD T-score less than −1.0 and greater than −2.5, and osteoporosis as T-score less than −2.5. Vertebrae with a BMD > 1 SD greater or less than the immediately adjacent vertebrae were excluded from the analyses, in accordance with the International Society for Clinical Densitometry rules for excluding individual vertebrae. For evaluating muscle mass, appendicular lean mass (ALM) was calculated as the sum of the lean mass for the legs and arms.

Follow-up BMD evaluations were conducted in 2010–2011. After excluding those who had died during the study period, refused to complete the follow-up evaluation, were lost to contact with the team, or had started taking drugs affecting bone metabolism, the BMD values for 339 (172 men and 167 women) people were analyzed to determine the rates of BMD loss and mortality.

2.4. Mortality

Mortality data were collected in an annual telephone call and were confirmed by data retrieved from the National Death Registry. The follow-up duration was defined as from the baseline evaluation until the date of death or the last follow-up in December 2014.

2.5. Statistical analyses

Values are shown as the mean ± SD. Baseline characteristics were compared according to their survival status in men and women using Student's *t*-test for continuous variables and the χ^2 test for categorical variables. Participants were followed longitudinally from the baseline to December 2014, or until the date of death. Hazard ratios (HRs) were analyzed for the baseline clinical parameters and BMD groups at each skeletal site. Mortality in the participants with low bone mass or osteoporosis group is expressed as the relative risk and 95% CI compared to normal BMD group using the Cox proportional-hazard model. In the multivariate model, covariates significantly associated with mortality in the univariate analyses were selected. Medical history, which may contribute to the BMD changes, was also included. Finally, age, BMI, ALM, creatinine, total cholesterol, hematocrit, albumin, SBP, HbA1c, and any history of malignancy, cerebrovascular attack, cardiovascular disease, or osteoporosis treatment were adjusted. Survival curves were estimated using a Kaplan–Meier survival curve. In the analyses about BMD changes and mortality, rapid bone loss was defined as an annualized bone loss rate > 1 SD of the gender-specific loss rate at each skeletal site, and HRs were calculated with covariates. The covariates were selected from those parameters that differed between the group with accelerated BMD loss and the control group. The model was then adjusted further for the conventional factors expected to affect mortality: model 1, unadjusted; model 2, adjusted for age; model 3, adjusted for age, BMI, and ALM; model 4, model 3 plus adjusted for total cholesterol, history of diabetes, any history of malignancy, cerebrovascular attack events, or cardiovascular diseases. All statistical analyses were performed using STATA software (version 14.0; StataCorp, College Station, TX, USA). Data with a value of $p < 0.05$ was considered significant.

3. Results

3.1. Baseline characteristics of the deceased and surviving participants

The mean follow-up duration was 7.3 years. During the follow up period, 74 men (23.3%) and 50 women (15.2%) died. Table 1 shows the baseline clinical characteristics of those who diet and survived. Compared with the survivors, the deceased participants were older and had a lower BMI in both men and women. Moreover, ALM was lower in the deceased men than in the surviving men. In regards to the laboratory parameters, the deceased participants had lower albumin level, and lower hemoglobin or hematocrit levels in both men and women. The deceased men had a lower total cholesterol level compared to survivors, and the deceased women had higher BUN and creatinine levels compared to surviving women. About the DXA parameters, the BMD and T scores were significantly lower and the prevalence of osteoporosis was

Table 1
Comparisons of baseline clinical characteristics between the deceased and survived subjects.

	Men							Women						
	Deaths during study			Alive throughout the study			*p*-Value	Deaths during study			Alive throughout the study			*p*-Value
N	74			244				50			280			
Age (years)	79.4	±	8.2	72.1	±	6.8	< 0.001	78.3	±	8.5	72.3	±	6.7	< 0.001
Height (cm)	164.1	±	6.3	165.0	±	5.9	0.252	149.2	±	6.4	150.8	±	5.4	0.066
Weight (kg)	62.7	±	10.2	65.8	±	9.6	0.018	52.4	±	10.5	56.1	±	8.6	0.009
BMI (kg/m^2)	23.2	±	3.3	24.1	±	3.2	0.038	23.4	±	3.8	24.6	±	3.3	0.028
ALM (kg)	17.70	±	2.80	18.90	±	2.50	0.001	12.78	±	4.41	12.86	±	1.69	0.84
SBP (mm Hg)	135.5	±	20.1	132.9	±	17.6	0.267	135.9	±	16.3	133.1	±	19.8	0.350
DBP (mm Hg)	83.6	±	12.2	83.3	±	10.5	0.798	85.1	±	11.4	83.4	±	11.7	0.351
BUN (mg/dL)	17.9	±	6.8	16.6	±	4.7	0.068	17.7	±	4.9	15.6	±	4.6	0.005
Creatinine (mg/dL)	1.3	±	0.3	1.2	±	0.2	0.079	1.1	±	0.2	1.0	±	0.2	0.013
Glucose (mg/dL)	111.1	±	23.5	114.2	±	27.2	0.370	103.8	±	18.8	107.3	±	23.7	0.334
HbA1c (%)	6.1	±	0.9	6.1	±	0.9	0.752	6.0	±	0.6	6.0	±	0.8	0.581
Total cholesterol (mg/dL)	183.9	±	31.0	196.4	±	39.9	0.014	210.6	±	33.1	210.5	±	36.7	0.977
Protein (mg/dL)	7.4	±	0.4	7.5	±	0.5	0.296	7.4	±	0.5	7.5	±	0.4	0.032
Albumin (mg/dL)	4.08	±	0.27	4.14	±	0.21	0.04	4.04	±	0.27	4.14	±	0.20	0.00
Hemoglobin (g/dL)	13.95	±	1.64	14.75	±	1.43	< 0.001	12.94	±	1.07	13.33	±	1.07	0.01
Hematocrit (%)	42.50	±	4.37	44.45	±	4.04	< 0.001	39.87	±	2.91	40.75	±	3.11	0.06
Lumbar spine BMD (g/cm^2)	1.096	±	0.219	1.199	±	0.660	0.186	0.801	±	0.182	0.900	±	0.156	< 0.001
Lumbar spine T-score	−0.7	±	1.8	−0.2	±	1.7	0.025	−2.6	±	1.5	−1.8	±	1.3	< 0.001
Femur neck BMD (g/cm2)	0.772	±	0.134	0.852	±	0.130	< 0.001	0.600	±	0.107	0.679	±	0.110	< 0.001
Femur neck T-score	−1.4	±	1.0	−0.8	±	1.0	< 0.001	−2.5	±	0.9	−1.9	±	0.9	< 0.001
Total hip BMD (g/cm2)	0.841	±	0.143	0.926	±	0.141	< 0.001	0.646	±	0.127	0.742	±	0.125	< 0.001
Total hip T-score	−0.8	±	1.1	−0.1	±	1.1	< 0.001	−2.4	±	1.0	−1.6	±	1.0	< 0.001
Osteoporosis/low bone mass/ normal (N,%)	112 (45.9%)/112 (45.9%)/20 (8.2%)			16 (21.6%)/38 (51.4%)/20 (27.0%)			< 0.001	23 (8.2%)/138 (49.3%)/119 (42.5%)			0 (0%)/15 (30.0%)/35 (70.0%)			< 0.001
T2DM (N,%)	32 (43.2%)			94 (38.4%)			0.452	12 (24.0%)			94 (33.6%)			0.182
Hypertension (N,%)	27 (36.5%)			101 (41.2%)			0.466	26 (52.0%)			131 (46.8%)			0.496
Cerebrovascular attack event (N,%)	7 (9.5%)			22 (9.0%)			0.901	8 (16.0%)			27 (9.6%)			0.210
Cardiovascular disease	2 (2.7%)			19 (7.8%)			0.123	4 (8%)			18 (6.4%)			0.682
Any previous malignancy (N, %)	7 (9.5%)			19 (7.8%)			0.639	5 (10.0%)			21 (7.5%)			0.356
Osteoporosis treatment	3 (4.1%)			1 (0.4%)			0.014	10 (20.0%)			74 (26.4%)			0.336
Fracture histories	7 (9.5%)			32 (13.1%)			0.401	6 (12.0%)			52 (18.6%)			0.261

Data were provided as mean + SD or N(%).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; BMD, bone mineral density; T2DM, type 2 diabetes mellitus.

significantly higher in the deceased participants than in the survivors in both men and women. A significantly higher percentage of subjects used anti-osteoporotics in the deceased group only in men (4.1% vs 0.4% in men, $p = 0.014$), but the fracture history did not differ significantly between the deceased and surviving groups in both men and women.

3.2. Baseline BMD and all-cause mortality

The associations between baseline clinical parameters and all-cause mortality are shown in Table 2. In men, older age was related to increased risk of mortality, whereas BMI > 25 kg/m^2, higher ALM, and higher total cholesterol, albumin, hematocrit, and hemoglobin levels were significantly associated with a lower risk of mortality. In women, older age and higher creatinine level were related to increased risk of mortality, and BMI > 25 kg/m^2 and higher albumin and hemoglobin levels were related to a lower risk.

We calculated the relative risk of mortality according to BMD group (normal, low bone mass, and osteoporosis) and per 1 SD decrease in BMD at each skeletal site. Compared with normal BMD, in men, low bone mass or osteoporosis, or 1 SD decrease in BMD at each skeletal site was a significant predictor of increased mortality in men. Similarly in women, osteoporosis in the lumbar spine, femoral neck, and total hip, or per 1 SD decrease in BMD in those regions was significantly related to increased risk of mortality (Table 2). Osteoporosis in the femoral neck was the strongest predictor of an increased risk of mortality in both men and women: 6.32-fold greater risk in men and 17.07-fold greater risk in women compared with the gender-matched normal BMD group. Kaplan–Meier survival curve analysis of all-cause mortality according to BMD group showed a divergence in mortality risk for all skeletal sites in both men and women (Fig. 1). The multivariable Cox proportional-hazards model (Table 3) confirmed that the baseline BMD was an independent predictor of increased all-cause mortality after adjusting for all confounders in men. Osteoporosis in the lumbar spine conferred a 2.81-fold greater risk in men. The mortality risks were 2.08-fold and 3.31-fold greater for men with low bone mass and osteoporosis in the femoral neck, respectively. For total hip BMD, low bone mass and osteoporosis conferred greater risks compared with normal BMD in men, but this was significantly only for low bone mass (HR 2.14, 95% CI 1.24–3.71, $p = 0.006$). Moreover, each 1 SD decrease in BMD was also associated with an increased risk of mortality in the adjusted model (HR 1.17 in the lumbar spine, HR 1.45 in the femur neck, and HR 1.40 in the total hip, $p < 0.05$, respectively). By contrast, in women, the association between low bone mass or osteoporosis and all-cause mortality was not significant in the multivariable model. However, each 1 SD increase in BMD in the lumbar spine and total hip was significantly associated with increased mortality in women. (HR 1.40 in the lumbar spine and HR 1.73 in the total hip, $p < 0.05$ for each) (Table 3). After further adjusting for the medical histories that are conventionally expected to contribute to the BMD changes including malignancy, cerebrovascular attack events or cardiovascular disease, the results were not different (Supplemental Table 1).

In the current study, 39 (12.3%) men and 58 (17.6%) women had a history of osteoporotic fracture. We also analyzed the associations

Table 2
Unadjusted HRs of clinical parameters and BMD for all-cause mortality during a follow period.

	Men						Women					
	HR	95% CI				p-Value	HR	95% CI				p-Value
Age (per 1 yr increase)	1.13	(1.09	–	1.17	)	< 0.001	1.10	(1.06	–	1.15	)	< 0.001
BMI, kg/m^2	0.92	(0.84	–	1.00	)	0.04	0.90	(0.82	–	0.99	)	0.03
< 18.5	0.83	(0.27	–	2.51	)	0.74	1.30	(0.32	–	5.25	)	0.71
18.5–23.0	Referent											
23–25	0.54	(0.28	–	1.04	)	0.07	0.63	(0.28	–	1.41	)	0.26
≥25.0	0.44	(0.23	–	0.85	)	0.01	0.48	(0.23	–	0.98	)	0.05
ALM (per 1 kg increase)	0.85	(0.77	–	0.93	)	< 0.001	0.98	(0.82	–	1.18	)	0.85
Creatinine (per 1 mg/dL increase)	2.46	(0.89	–	6.82	)	0.08	6.23	(1.41	–	27.6	)	0.02
HbA1c (per 1% increase)	0.95	(0.71	–	1.28	)	0.95	0.89	(0.58	–	1.36	)	0.58
Total cholesterol (per 1 mg/dL increase)	0.99	(0.98	–	1.00	)	0.02	1.00	(0.99	–	1.01	)	0.98
Albumin (per 1 mg/dL increase)	0.29	(0.09	–	0.93	)	0.04	0.10	(0.02	–	0.43	)	< 0.001
Hemoglobin (per 1 increase)	0.80	(0.72	–	0.89	)	< 0.001	0.74	(0.58	–	0.95	)	0.02
Hematocrit (per 1 increase)	0.93	(0.89	–	0.97	)	< 0.001	0.92	(0.84	–	1.00	)	0.06
SBP (per 1 mm Hg increase)	1.01	(0.99	–	1.02	)	0.27	1.01	(0.99	–	1.02	)	0.35
T2DM	1.22	(0.72	–	2.07	)	0.45	0.62	(0.31	–	1.25	)	0.18
Hypertension	0.82	(0.48		1.40	)	0.47	1.23	(0.68		2.25	)	0.50
Cerebrovascular attack event	0.89	(0.35	–	2.30	)	0.82	1.78	(0.76	–	4.19	)	0.18
Cardiovascular disease	0.33	(0.74		1.44	)	0.14	1.27	(0.41		3.91	)	0.68
Any previous malignancy	1.24	(0.50	–	3.08	)	0.64	1.37	(0.49	–	3.82	)	0.55
Lumbar spine BMD												
Normal	Referent											
Low bone mass	1.65	(0.92	–	2.96	)	0.10	1.71	(0.65	–	4.51	)	0.28
Osteoporosis	3.74	(1.69	–	8.30	)	< 0.001	3.32	(1.30	–	8.52	)	0.01
BMD (per 1 SD decrease)	1.17	(1.01	–	1.35	)	0.02	1.52	(1.23	–	1.87	)	< 0.001
Femur neck BMD												
Normal	Referent											
Low bone mass	3.25	(1.80	–	5.87	)	< 0.001	5.99	(0.79	–	45.6	)	0.08
Osteoporosis	6.32	(2.38	–	16.77	)	< 0.001	17.07	(2.24	–	130.4	)	0.01
BMD (per 1 SD decrease)	1.69	(1.35	–	2.11	)	< 0.001	1.95	(1.48	–	2.6	)	< 0.001
Total hip BMD												
Normal	Referent											
Low bone mass	3.46	(1.97	–	6.07	)	< 0.001	2.67	(0.89	–	8.00	)	0.08
Osteoporosis	3.02	(0.69	–	13.16	)	0.14	7.29	(2.38	–	22.3	)	< 0.001
BMD (per 1 SD decrease)	1.59	(1.29	–	1.95	)	< 0.001	1.99	(1.55	–	2.6	)	< 0.001

HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; BMD, bone mineral density; T2DM, type 2 diabetes mellitus; ALM, appendicular lean mass.

between BMD and mortality after excluding participants with a history of fracture, and the results were similar to those including participants with a history of fracture (Supplemental Table 2).

3.3. BMD loss and mortality rates

At the follow-up evaluation, 172 men and 167 women received the second DXA evaluation, and we analyzed the association between a rapid rate of bone loss and mortality during the follow-up period in these participants. The annual mean percent BMD changes in men were −0.23% for the lumbar spine, −0.28% for the femoral neck, and −0.64% for the total hip. The respective changes in women were 0.17%, −0.74%, and −0.91% (Table 4). Accelerated BMD loss group based on total hip BMD, that was defined as an annualized bone loss rate was > 1 SD of the gender-specific loss rate, were older, had lower ALM value, and have lower glucose levels or cholesterol levels, and had higher rates of diabetes and malignancy in men. Moreover, they showed lower BMD levels for all three skeletal sites compared to group with 'expected BMD loss/BMD maintain group'. The mortality rate was also significantly higher in group with accelerated BMD loss than group without accelerated BMD loss (5.04% vs 16.0%, $p = 0.018$). However, in women, there were no differences in both baseline characteristics and mortality rates between those two groups (Supplemental Table 3).

In men, in the unadjusted model (model 1), age-adjusted model (model 2), and age-, BMI-, and ALM adjusted model (model 3), and after further adjusting for other clinical confounders (model 4), rapid BMD loss in the lumbar spine, femoral neck, and total hip was a strong significant predictor of increased mortality. In women, accelerated BMD loss in the femoral neck was significantly related to mortality or showed marginal significances in models 1–4, but BMD loss rates in the lumbar spine and total hip were not related to mortality (Table 5).

4. Discussion

This study demonstrates that lower baseline BMD and faster BMD loss rate were associated with increased risk of mortality in an elderly population from a prospective study of community-dwelling older adults; lower BMD, indicating low bone mass or osteoporosis, in the lumbar spine, femoral neck, and total hip were found to be associated with increased risk of all-cause mortality in both men and women, but the significance remained after controlling for age, BMI, and other potential confounders only in men. Moreover, faster BMD loss in men also significantly related to the higher risk of death.

Several previous studies have confirmed a significant relationship between BMD and overall mortality in elderly populations [13,14]. Although the exact mechanisms underlying the relationship between BMD and death are unclear, there are a few plausible explanations for this association. Lower BMD may reflect the potential for osteoporotic fracture, which increases the risk of mortality in older people [15,16]. Therefore, a higher rate of fracture events may be one factor that contributes to a higher mortality risks in people with lower BMD. In addition, lower BMD was associated with increased risk of all-cause mortality and cardiovascular mortality as well after controlling confounders related to cardiovascular risk [17–19]. These studies suggest that impaired bone strength, as indicated by lower BMD, may be the parameter about the risk of atherosclerosis [20].

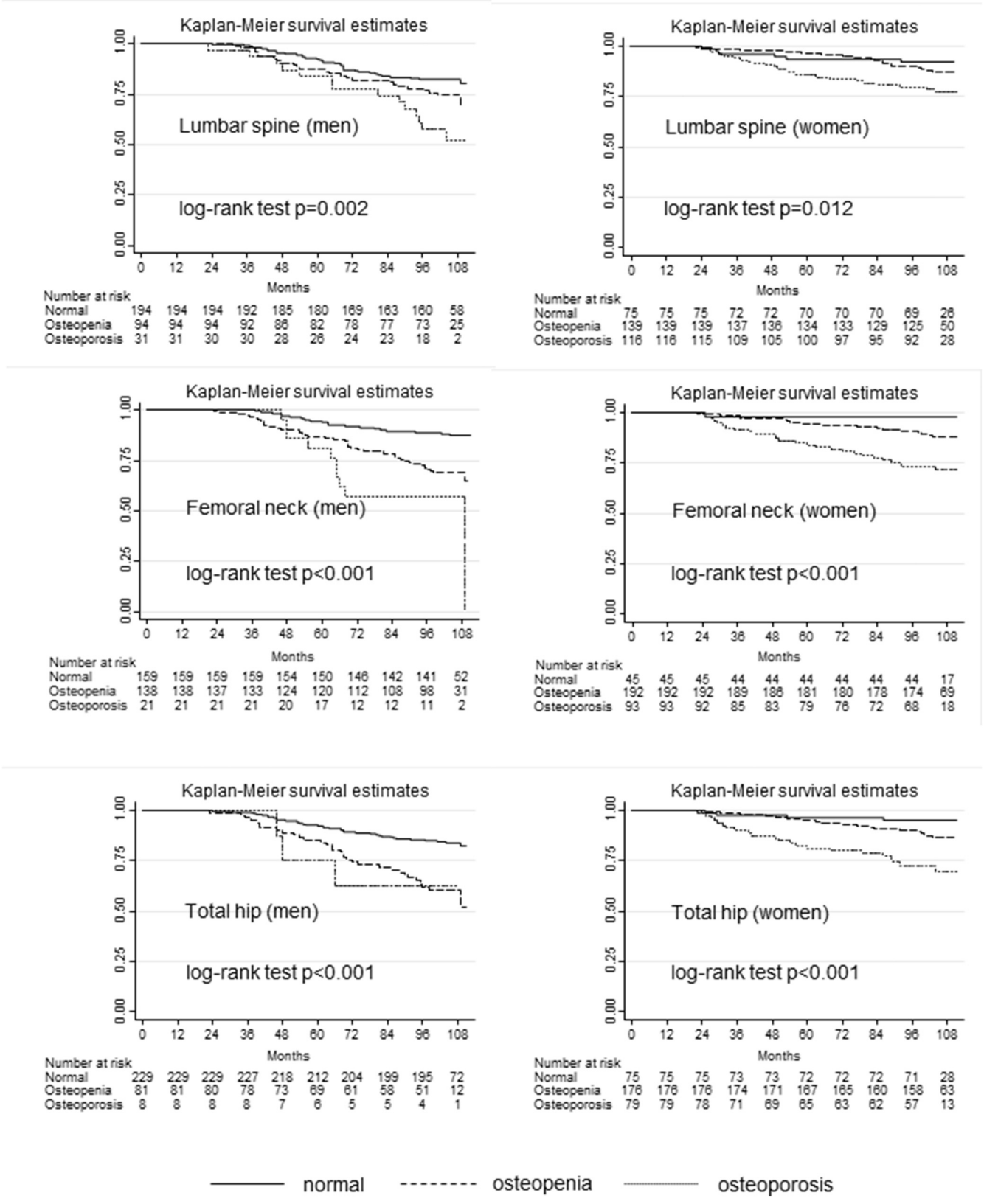

Fig. 1. Kaplan-Meire survival curve for BMD status in men and women each skeletal site.

Lower BMD values in the elderly can be caused by many clinical factors. Lower physical activity level and thus, lower lean body mass (sarcopenia), are risk factors for lower bone mass [21–23]. Sarcopenia is a well-known risk factor for increased mortality in elderly population [24,25]. Therefore, diminished bone mass together with a deficit in lean mass may partially contribute to the link between BMD and mortality. However, in another study, the associations between BMD and mortality remained significant after adjusting for lean body mass and

Table 3
Cox proportional-hazard ratio of all-cause mortality by BMD WHO classification in each skeletal site.

	Men							Women						
	Adjusted HR*	95% CI					*p*-Value	Adjusted HR*	95% CI					*p*-Value
Model 1														
Normal	Referent													
Lumbar spine														
Low bone mass	1.71	(	0.99	–	2.99	)	0.055	1.47	(	0.52	–	4.14	)	0.464
Osteoporosis	2.81	(	1.39	–	5.65	)	0.004	2.17	(	0.75	–	6.29	)	0.153
BMD (per 1 SD decrease)	1.17	(	1.01	–	1.37	)	0.047	1.40	(	1.02	–	1.94	)	0.040
Femur neck														
Low bone mass	2.08	(	1.14	–	3.81	)	0.017	4.11	(	0.55	–	30.93	)	0.169
Osteoporosis	3.31	(	1.37	–	7.99	)	0.008	6.28	(	0.78	–	50.43	)	0.084
BMD (per 1 SD decrease)	1.46	(	1.10	–	1.94	)	0.008	1.44	(	0.90	–	2.32	)	0.132
Total hip														
Low bone mass	2.14	(	1.24	–	3.71	)	0.006	3.50	(	0.79	–	15.40	)	0.097
Osteoporosis	1.76	(	0.88	–	10.59	)	0.078	4.28	(	0.78	–	23.42	)	0.093
BMD (per 1 SD decrease)	1.40	(	1.09	–	1.82	)	0.009	1.73	(	1.09	–	2.75	)	0.020

HRs* adjusted for age, BMI, ALM, creatinine, total cholesterol, albumin, hematocrit and osteoporosis treatment.
HR, hazard ratio; CI, confidence interval.

Table 4
Baseline characteristics and annualized percent changes at each skeletal site in subjects who performed second BMD evaluation.

	Men			Women		
	(N = 172)			(N = 166)		
Age (years)	71.3	±	6.5	70.4	±	5.3
BMI (kg/m^2)	24.4	±	3.0	24.6	±	3.0
HbA1c (%)	6.1	±	1.0	6.1	±	0.8
Creatinine (mg/dL)	1.2	±	0.2	1.0	±	0.2
Total cholesterol (mg/dL)	197.0	±	37.2	210.0	±	36.7
Albumin (mg/dL)	4.2	±	0.2	4.2	±	0.2
SBP (mm Hg)	134.2	±	17.1	132.2	±	19.7
DBP (mm Hg)	84.5	±	10.4	83.4	±	12.4
Annualized percent changes of BMD (%/year)						
Lumbar spine	−0.23	±	2.86	0.17	±	1.75
Femur neck	−0.28	±	1.35	−0.74	±	1.62
Total hip	−0.64	±	1.09	−0.91	±	1.40

Data were provided as mean + SD.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMD, bone mineral density.

mobility [26]. That is, low physical activity level and lower lean mass do not fully explain the associations between BMD and mortality. Furthermore, it is becoming evident that bone plays other extraskeletal roles as an endocrine organ, for example in energy homeostasis [8]. Therefore, lower bone mass may also negatively affects extraskeletal homeostasis in the human body [27]. Vitamin D insufficiency and other chronic conditions or medications that affect negatively bone mass, may also contribute in the association between BMD and increased mortality [28,29]. Furthermore, nutritional status also contributes to both mortality and BMD in the elderly population. In the present study, serum levels of total cholesterol, albumin, hemoglobin, and hematocrit, which are indirect indicators of nutritional status, were independently associated with increased mortality. Hematocrit level was also positively associated with BMD (data were not shown). However, even after further adjusting for these parameters, BMD was an independent predictor of future mortality. Consequently, it is possible that lower BMD is a marker of impaired general health and an increased risk of overall mortality in elderly people.

In addition to the baseline BMD, a faster decline in BMD was shown in our study to be an independent risk factor for increased mortality regardless of baseline BMD, especially in men. Rapid bone loss can indicate general weakness, acute illness, or chronic inflammation [30,31]. That is, rapid bone loss may reflect the presence of these conditions which can make elderly to be vulnerable to other medical

Table 5
HRs of rapid bone loss[a] for all-cause mortality in each skeletal site.

	Lumbar spine							Femur neck							Total hip						
	HR	95% CI					*p*-Value	HR	95% CI					*p*-Value	HR	95% CI					*p*-Value
Men																					
Model 1	8.35	(	1.76	–	39.58	)	0.008	5.37	(	1.68	–	17.16	)	0.005	8.69	(	2.70	–	27.95	)	< 0.001
Model 2	9.48	(	1.49	–	60.44	)	0.017	4.41	(	1.20	–	16.25	)	0.026	4.96	(	1.34	–	18.34	)	0.016
Model 3	10.63	(	1.51	–	74.90	)	0.018	5.04	(	1.16	–	21.90	)	0.031	5.07	(	1.30	–	19.79	)	0.019
Model 4	9.94	(	1.41	–	70.27	)	0.021	5.87	(	1.24	–	28.20	)	0.027	4.41	(	1.11	–	17.53	)	0.033
Women																					
Model 1	1.93	(	0.38	–	9.81	)	0.428	4.81	(	1.24	–	18.60	)	0.023	2.76	(	0.66	–	11.50	)	0.164
Model 2	1.44	(	0.25	–	8.18	)	0.682	3.89	(	0.94	–	15.99	)	0.060	1.84	(	0.37	–	9.23	)	0.456
Model 3	1.62	(	0.27	–	9.66	)	0.596	5.13	(	1.11	–	23.78	)	0.037	2.03	(	0.36	–	10.68	)	0.404
Model 4	1.99	(	0.32	–	12.21	)	0.453	6.34	(	1.28	–	31.40	)	0.024	2.36	(	0.43	–	13.04	)	0.326

Model 1. Unadjusted.
Model 2. Age adjusted.
Model 3. Age, BMI and ALM adjusted.
Model 5. Age, BMI, ALM, total cholesterol, histories of diabetes, any histories of malignancy, cerebrovascular attack event and cardiovascular diseases adjusted.
[a] Rapid bone loss was defined as an annualized bone loss rate > 1 SD of the gender-specific loss rate at each skeletal site.

events [32]. Although we cannot draw conclusion about the causality in this prospective cohort study, previous findings and the present results suggest that slower bone loss may indicate better health conditions and lower the risk of mortality in community-dwelling elderly people.

In our study, although the lower BMD or faster decline in BMD were associated with increased mortality risk in the unadjusted analyses, there relationships were no longer significant in women in the multivariate model. There are several studies that have reported gender-specific associations between BMD and mortality, and the differential effects of covariates for BMD and mortality may contribute this sexual dimorphism [13]. In women, BMD T scores provide stronger association with age, than in men, thus BMD parameters may not retain statistical significance with respect to mortality after further adjusting age. Moreover, the mortality rate is generally lower in women compared with men, and it was 23.3% in men and 15.2% in women in our study. Therefore, the lower mortality rate, and thus sample size, in women may have limited our ability to find a significant effect in the adjusted model. Further studies with large samples are needed to elucidate whether the link between BMD and morality is gender-specific or not.

To date, there is no convincing evidence that increasing BMD will decrease overall mortality in the general population. However, a few studies have shown that administration of antiosteoporotic drugs may be associated with beneficial effects on mortality in treated compared with untreated patients; in one previous study, using bisphosphonates are significantly decreased risk of mortality [33]. In another study, use of raloxifene was associated with reduced mortality after 12 years [34]. However, it is unclear whether the beneficial effects of these medications that aim to increase bone mass relate to their pharmacological efficacy beyond skeletal benefits or to increased BMD per se.

There are several limitations of this study. One limitation is the limited sample size from a population that was not originally drawn to investigate the relationship between BMD and mortality in the elderly population. Second, only participants who completed the follow-up evaluations were included in this study, and those who had not completed the follow-up DXA, had died, or been censored were excluded from the analysis. A high percentage of participants—146 (45.9%) men and 164 (49.7%) women—did not participate in the follow-up DXA assessments. The mortality rate was significantly higher in the group without follow-up DXA evaluations compared with that with follow-up evaluations (41.4% vs 14% in men, 24.4% vs 6.02% in women, respectively, $p < 0.001$). It is possible that BMD loss was faster in the deceased participants, who did not have follow-up DXA assessment, than in surviving participants. Therefore, this type of selection bias may have led to underestimation of the effects of bone loss on mortality. Third, we analyzed only all-cause mortality, and not cause-specific mortality including fracture-related, because of the small sample size. Fourth, aspects of the medical history expected to affect BMD or mortality were obtained by questionnaire and therefore have limited accuracy.

In conclusion, we report that both lower baseline BMD and a faster decline in BMD were associated with excess morality in a community-dwelling elderly population, especially in men. The exact mechanisms underlying this link between low bone mass and mortality are not clear, but this study suggests that lower bone mass and faster bone loss may be markers of poorer health, which may contribute to the risk of mortality. Whether therapeutic interventions to reverse diminished bone mass or prevent greater loss are effective remains to be elucidated. Our findings suggest that efforts to maintain bone health status are needed in the elderly population.

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Authors contributions

KMK designed the study, and SL, JYL, KWK and HCJ collected the data. KMK, SL and HCJ analyzed the data. KMK, SL, SHC and HCJ interpreted the data. JHM, JYL and KWK assisted with data collection. KMK and HCJ drafted the manuscript. SHC, JHM and KWK reviewed the manuscript and edited the manuscript. HCJ is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors agreed on the final content of the manuscript.

Conflict of interest

All authors state that they have no conflicts of interest.

Sponsor's role

The funding sources played no roles in the design, conduct, or reporting of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.01.017.

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