Journal of Bone and Mineral Metabolism (2019) 37:835–843
https://doi.org/10.1007/s00774-018-0980-6

ORIGINAL ARTICLE

Metabolic characteristics of subjects with spine–femur bone mineral density discordances: the Korean National Health and Nutrition Examination Survey (KNHANES 2008–2011)

A Ram Hong[1] · Jung Hee Kim[2] · Ji Hyun Lee[2] · Sang Wan Kim[2,3] · Chan Soo Shin[2]

Received: 20 June 2018 / Accepted: 16 November 2018 / Published online: 3 January 2019

Abstract
The diagnosis of osteoporosis is determined based on the lowest bone mineral density (BMD) T-score at the lumbar spine (LS) and hip. However, there are occasional marked discordances between the T-score of LS and femur neck (FN). We aimed to examine the prevalence and characteristics of individuals with spine–femur BMD discordance using a nationwide survey. A total of 3233 men aged ≥ 50 years and 2915 postmenopausal women were included from the Korean National Health and Nutrition Examination Surveys (2008–2011). The spine–femur discordance was defined as a difference of ≥ 1.5 SD between LS and FN BMD. Subjects were divided into three groups: low LS (LS < FN), low FN (LS > FN), and no discordance. Four-hundred and seventeen men (12.9%) and two hundred and ninety women (10%) exhibited spine–femur BMD discordance. The prevalence of hypertension and diabetes was higher in men and women with low FN BMD than in any other group. Fasting plasma glucose and homeostasis model assessment of insulin resistance was the highest in subjects with low FN BMD among the three groups. Low FN BMD revealed higher serum parathyroid hormone and lower 25-hydroxyvitamin D3 levels compared to any other group in women, but this was not observed in men. Osteoporosis was prevalent in subjects with discordance in both genders, particularly, in those with low LS BMD (31.6% in men and 63.5% in women). Given the high prevalence of spine–femur BMD discordance, low FN BMD may be associated with vitamin D deficiency and insulin resistance, but low LS BMD may present severe osteoporosis.

Keywords Spine–femur discordance · Bone mineral density · T-score · Osteoporosis

Introduction

According to the World Health Organization (WHO) criteria, osteoporosis is defined as the lowest bone mineral density (BMD) T-score of ≤ −2.5 measured at the lumbar spine (LS) or hip sites [1, 2]. BMD is the most commonly used modality for the prediction of a fracture risk; a BMD decrease of 1 standard deviation (SD) increases the fracture risk by 1.5-fold to 2.0-fold [3].

Although LS and femur neck (FN) BMD are closely correlated, a significant proportion of the population has different T-score levels (normal, osteopenia, and osteoporosis) at LS and FN [4, 5]. T-score discordance between LS and FN is classified into major and minor [6]. Major discordance refers to osteoporosis at one site, with normal bone mass at the other site. Minor discordance refers to a small difference between the two sites, indicating osteoporosis at one site and osteopenia at the other site, or osteopenia at one site and normal bone mass at the other site. Woodson et al. suggested the following five reasons for discordance between the spine and hip sites: physiologic factors, pathological factors, anatomical factors, artifacts, and technical problems [6]. Furthermore, the risk factors affecting BMD discordance were recently identified to be age, obesity, menopause, premature menopause, and multiple pregnancies [7, 8].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00774-018-0980-6) contains supplementary material, which is available to authorized users.

✉ Chan Soo Shin
csshin@snu.ac.kr

1 Department of Internal Medicine, Chonnam National University Medical School, Gwangju, South Korea

2 Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea

3 Department of Internal Medicine, Seoul Metropolitan Government Boramae Medical Center, Seoul, South Korea

The previous studies on spine–femur BMD discordance have focused on the prevalence and the impact of the discordance on the management of osteoporosis and fractures [8–12]. However, metabolic characteristics of subjects with spine–femur BMD discordance are not well known. Therefore, we investigated the clinical and biochemical characteristics of subjects with discordance between the T-scores of LS and FN BMD in Koreans using nationwide survey data.

Materials and methods

Study population

The Korea National Health and Nutrition Examination Surveys (KNHANES) is a nationwide survey representing the non-institutionalized civilian Korean population, which has been conducted by the South Korean Centers for Disease Control and Prevention since 1998. We recruited study subjects in KNHANES IV and V (2008–2011). The survey consists of three individual surveys: Health Interview Survey, Health Examination Study, and Nutrition Survey. A stratified, multistage, and clustered probability sampling method was used based on geographical area, age, and gender. A total of 9308, 10,078, 8473, and 8518 subjects were included in KNHANES in 2008, 2009, 2010, and 2011, respectively, and the response rates were 74.3, 79.2, 77.5, and 80.4%, respectively. The details of KNHANES IV and V were previously published [13, 14].

The initial candidates for this study were 19,158 participants who underwent dual-energy X-ray absorptiometry (DXA). Subjects whose DXA data were inadequate for analysis ($n=1896$) and men aged < 50 or premenopausal women ($n=8621$) were excluded. In addition, we excluded subjects who were taking anti-osteoporosis medications, such as bisphosphonate, selective estrogen receptor modulator, and estrogen therapy ($n=871$). Furthermore, subjects with chronic renal failure, chronic hepatitis B or C, liver cirrhosis, thyroid disease, rheumatoid arthritis, and malignancy were excluded ($n=1622$). Finally, a total of 3233 men ≥ 50 years and 2915 postmenopausal women were analyzed. The flow diagram of study participants is presented in Fig. 1.

All KNHANES surveys were reviewed and approved by the Institutional Review Board of the Korea Center for Disease Control and Prevention (IRB Nos. 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21, and 2011-02CON-06-C), and all participants provided informed consent prior to enrollment in the survey. Because the KNHANES data set is publicly available, the additional institutional review board approval was waived in this study. The study was conducted in accordance with the Declaration of Helsinki.

Health questionnaires for lifestyle and comorbidity assessment

Demographic factors and health behaviors of subjects were collected through household interviews. Cigarette smoking status was categorized as none, ex-smoker, and current smoker, and was defined as patients smoking at least five cigarettes daily in the previous 12 months. Alcohol consumption was classified as none, ex-drinker, and current drinker, and was defined as drinking alcohol at least once per

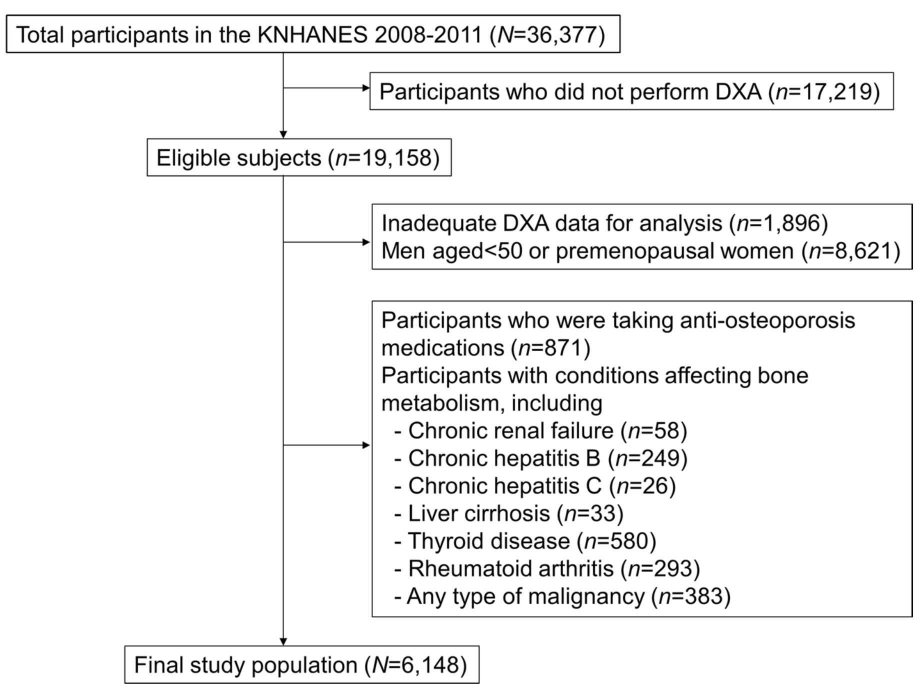

Fig. 1 Flow diagram of the study subjects

month in the previous 12 months. Physical activity (PA) was determined by asking participants how often they exercised each week using the Korean version of the International Physical Activity Questionnaire. An average metabolic equivalent (MET) score was derived for each type of activity using the compendium by Ainsworth et al.: 3.3 METs for walking, 4.0 METs for moderate PA, and 8.0 METs for vigorous PA [15]. Accordingly, the total PA (MET × min/week) was defined as the sum of the weekly METs of walking, moderate PA, and vigorous PA. The 24-h dietary recall method was used to collect amount of daily calcium intake of participants. In addition, we collected information on the participants' medical history of hypertension, diabetes mellitus, coronary artery disease (angina and myocardial infarction), and cerebrovascular events via a questionnaire.

Measurement of anthropometric parameters and BMD

All participants underwent a standardized physical examination. Body weight (kg) and height (cm) were measured using the standard protocols, with subjects dressed in light clothing without shoes. Body mass index (BMI) was calculated as body weight divided by the square of the height in meters (kg/m^2).

Areal BMD (g/cm^2) was measured using DXA (QDR4500A, Hologic Inc., Waltham MA, USA) at mobile examination centers and operated by licensed, trained technicians. DXA instruments were calibrated as previously described [16], and reference values of the National Health and Nutrition Examination Survey were obtained using this calibration method [17]. We maintained DXA calibrations via an internal referencing system and daily measured spine phantoms. BMD measurements of LS (L1-4), FN, and the total hip (TH) were analyzed using the standard techniques of the Korean Society of Osteoporosis and Hologic Discovery software (version 13.1).

The difference in the discordance between LS and FN BMD was defined as ≥ 1.5 SD, and was divided into two groups: low LS (LS < FN) and low FN (LS > FN). According to the WHO criteria, the diagnosis of osteoporosis, osteopenia, and normal bone mass was determined by the following T-scores: ≤ −2.5, −2.5 to 1.0, and > −1.0, respectively.

Measurement of biochemical parameters

Blood samples were collected from all participants in the morning after at least 8 h of fasting. Samples were drawn from the antecubital vein, and were immediately refrigerated and centrifuged. Fasting plasma glucose (FPG), total cholesterol, triglyceride, high-density lipoprotein cholesterol, blood urea nitrogen, and creatinine were measured using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). Serum low-density lipoprotein cholesterol was calculated using the Friedewald equation [18]. Fasting insulin was measured using an immunoradiometric assay (1470 Wizard γ-counter; PerkinElmer). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as previously described [19]. Serum 25-hydroxyvitamin D3 [25(OH) D] level (ng/mL) was measured using a radioimmunoassay (DiaSorin Inc., Stillwater, MN, USA) using a 1470 Wizard γ-counter (PerkinElmer, Turku, Finland). Serum intact parathyroid hormone (PTH) was measured using N-tact PTH assay with LIAISON (DiaSorin Inc., Stillwater, MN, USA) by chemiluminescence immunoassay method.

Statistical analysis

All measurements were reported as the mean ± standard deviation (SD) or *n* (%). Clinical characteristics of the low LS, low FN, and no discordance groups were compared using the analysis of variance (ANOVA). The correlation analyses between BMD at three skeletal sites were performed using Pearson's correlation. Partial correlation analyses were used to extract the correlation coefficient after adjusting for age and BMI. We used the analysis of covariance (ANCOVA) to compare biochemical parameters after adjusting for confounders between the three groups. Bonferroni correction was adopted as a post hoc analysis to account for the multiple testing issues. All statistical analyses were performed using SPSS statistics for Windows (Version 21, IBM Corp., Armonk, NY, USA), and a P value of < 0.05 was considered to be statistically significant.

Results

Clinical characteristics of the study population

The clinical characteristics of the study participants are presented in Table 1 for men and Table 2 for women. The prevalence of spine–femur T-score discordance was 12.9% (417/3233) in men and 10% (290/2915) in women. Subjects in the low FN group were significantly older than those in the low LS and no discordance group among both men and women (both $P < 0.001$). The low FN group was associated with high BMI and waist circumference in men and women (all $P < 0.05$). PA was the highest in the low LS group in both genders ($P = 0.027$ in men and $P < 0.001$ in women). Hypertension and diabetes mellitus were more prevalent in the low FN group in men (both $P < 0.001$) and women ($P < 0.001$ and $P = 0.014$, respectively) than those in the other two groups. In addition, cerebrovascular events were frequently observed in the low FN group in men ($P < 0.001$). Subjects in the low FN group exhibited the lowest prevalence of current smoking and drinking status in men ($P = 0.002$

Table 1 Clinical characteristics of subjects with and without spine–femur T-score discordance in men ($n = 3233$)

	Low LS ($n = 152$, 4.7%)	Without discordance ($n = 2816$, 87.1%)	Low FN ($n = 265$, 8.2%)	*P*	*P**
Age (year)	60.2 ± 8.1	62.9 ± 8.7	68.0 ± 8.8	< 0.001	a, b, c
Height (cm)	166.3 ± 5.3	166.6 ± 5.9	166.8 ± 5.9	0.733	
Bwt (kg)	65.4 ± 10.5	65.8 ± 9.6	67.8 ± 9.4	0.004	b, c
BMI (kg/m^2)	23.6 ± 3.4	23.7 ± 2.9	24.3 ± 2.8	0.002	b, c
WC (cm)	84.3 ± 9.0	85.2 ± 8.6	87.5 ± 8.4	< 0.001	b, c
Current smoker, *n* (%)	64 (42.1)	907 (32.2)	67 (25.3)	0.002	
Current drinker, *n* (%)	98 (64.5)	1961 (69.6)	164 (61.9)	0.017	
Physical activity (MET × min/week)	4403 ± 5836	3427 ± 4648	3156 ± 4849	0.027	a, b
Daily calcium intake (mg)	580.4 ± 514.0	544.8 ± 356.3	491.1 ± 324.7	0.039	
Prevalent fracture, *n* (%)	12 (7.9)	179 (6.4)	11 (4.2)	0.253	
Hypertension, *n* (%)	35 (23.0)	1026 (36.4)	135 (50.9)	< 0.001	
Diabetes mellitus, *n* (%)	20 (13.2)	417 (14.8)	68 (25.7)	< 0.001	
Coronary arterial disease, *n* (%)	4 (2.6)	145 (5.1)	14 (5.3)	0.378	
Cerebrovascular disease, *n* (%)	3 (2.0)	111 (3.9)	26 (9.8)	< 0.001	
BMD T-score					
Lumbar spine	− 2.03 ± 1.11	− 0.79 ± 1.13	1.19 ± 1.15	< 0.001	a, b, c
Femur neck	− 0.22 ± 1.07	− 0.82 ± 0.95	− 0.95 ± 0.97	< 0.001	a, b

Data are presented as mean ± SD or *n* (%)

BMI body mass index, *WC* waist circumference

*Post hoc analysis using Bonferroni correction: a, $P < 0.05$ between low LS and without discordance; b, $P < 0.05$ between low LS and low FN; c, $P < 0.05$ between without discordance and low FN

Table 2 Clinical characteristics of subjects with and without spine–femur T-score discordance in women ($n = 2915$)

	Low LS ($n = 159$, 5.5%)	Without discordance ($n = 2625$, 90.0%)	Low FN ($n = 131$, 4.5%)	*P*	*P**
Age (year)	62.9 ± 8.8	64.0 ± 9.8	67.5 ± 10.3	< 0.001	b, c
Height (cm)	153.1 ± 5.4	153.0 ± 6.0	152.2 ± 5.9	0.317	
Bwt (kg)	56.7 ± 8.5	56.6 ± 8.9	58.3 ± 8.7	0.102	
BMI (kg/m^2)	24.2 ± 3.2	24.2 ± 3.3	25.2 ± 3.6	0.003	b, c
WC (cm)	81.9 ± 9.6	82.6 ± 9.4	85.4 ± 10.2	0.002	b, c
Current smoker, *n* (%)	5 (3.1)	112 (4.3)	7 (5.3)	0.649	
Current drinker, *n* (%)	44 (27.7)	641 (24.4)	30 (22.9)	0.590	
Physical activity (MET × min/week)	4216 ± 6907	2540 ± 4177	1663 ± 2560	< 0.001	a, b
Daily calcium intake (mg)	396.6 ± 292.9	406.2 ± 401.2	373.7 ± 249.3	0.657	
Prevalent fracture, *n* (%)	9 (5.7)	180 (6.9)	6 (4.6)	0.516	
Hypertension, *n* (%)	62 (39.0)	1006 (38.3)	79 (60.3)	< 0.001	
Diabetes mellitus, *n* (%)	17 (10.7)	397 (15.1)	30 (22.9)	0.014	
Coronary arterial disease, *n* (%)	5 (3.1)	97 (3.7)	5 (3.8)	0.934	
Cerebrovascular disease, *n* (%)	6 (3.8)	86 (3.3)	7 (5.3)	0.428	
BMD T-score					
Lumbar spine	− 2.87 ± 1.07	− 1.87 ± 1.16	− 0.27 ± 1.13	< 0.001	a, b, c
Femur neck	− 1.00 ± 1.07	− 1.77 ± 1.02	− 2.25 ± 1.08	< 0.001	a, b, c

Data are presented as mean ± SD or *n* (%)

BMI body mass index, *WC* waist circumference

*Post hoc analysis using Bonferroni correction: a, $P < 0.05$ between low LS and without discordance; b, $P < 0.05$ between low LS and low FN; c, $P < 0.05$ between without discordance and low FN and $P = 0.017$, respectively) but not in women ($P = 0.649$ and $P = 0.590$, respectively). Low calcium intake was associated with the low FN group only in men ($P = 0.039$).

In this study, 430 (85.1%) of 505 men with diabetes and 382 (86.0%) of 444 women with diabetes were receiving anti-diabetic medication or insulin therapy. There were no significant differences in BMD of all skeletal sites according to the use of anti-diabetic drugs. The proportion of subjects with spine–femur discordance also did not differ according to the use of anti-diabetic drugs (data not shown).

Correlation analysis between skeletal parameters

We carried out correlation analyses between BMD at three skeletal sites. TH BMD was inversely correlated with age and showed a positive correlation with BMI. TH BMD was positively correlated with LS and FN BMD after adjusting for age and BMI in both genders, with a stronger relationship in FN BMD than in LS BMD. When we performed correlation analyses in subgroup with no discordance, similar trend was observed. However, in subgroup analyses with discordance, a greater reduction in the magnitude of relationship between TH and LS BMD was observed, while the relationship between TH and FN BMD remained similar in both genders (Supplementary Tables 1 and 2).

Comparison of biochemical parameters in subjects with and without spine–femur discordance

We compared parameters with respect to glucose metabolism and calcium homeostasis according to the presence of spine–femur discordance (Table 3). FPG and HOMA-IR were highest in the low FN group both in men ($P = 0.005$ and $P < 0.001$, respectively) and women ($P = 0.048$ and $P = 0.020$, respectively). In addition, serum insulin level was the highest in the low FN group in men ($P = 0.035$) but not in women ($P = 0.315$). No significant differences were observed in lipid profiles between the three groups in men, while serum triglyceride was the highest in the low FN group in women ($P = 0.047$). Serum PTH levels were higher in the low FN group than in the low LS or no discordance group in unadjusted models in both genders (data not shown). However, statistical significance was observed only in women after adjusting for confounders ($P = 0.001$). Serum 25(OH)D level was the lowest in the low FN group ($P = 0.027$) in women but not in men ($P = 0.750$). Serum creatinine levels were significantly higher in the low FN group in both genders (all $P < 0.001$).

Prevalence of osteoporosis in the study subjects

Figure 2 presents the prevalence of osteoporosis, osteopenia, and normal BMD in subjects with and without spine–femur discordance. The overall prevalence of osteoporosis was 7.9% (254/3233) in men and 39.4% (1148/2915) in women. Osteoporosis was more prevalent in subjects with spine–femur discordance in both men and women (15.1% vs 6.8% in men and 55.2% vs. 37.6% in women); in particular, a higher prevalence of osteoporosis was observed in the low LS group than in the low FN group (31.6% vs. 5.7% in men and 63.5% and 45% in women; both $P < 0.05$).

Discussion

To the best of our knowledge, this is the first study to examine the characteristics of individuals with spine–femur BMD discordance with respect to metabolic profiles. In this general population-based study, 12.9% of men ≥ 50 years old and 10% of postmenopausal women had a BMD difference of ≥ 1.5 SD between LS and FN. We observed significantly higher FPG and HOMA-IR in subjects with low FN than in those with low LS or no discordance after adjusting for confounders. In addition, the prevalence of diabetes and hypertension was high in the low FN BMD group. Moreover, subjects with low FN BMD showed higher serum PTH and lower 25(OH)D levels than those with low LS BMD or no discordance. Osteoporosis was more prevalent in subjects with low LS BMD than in those with low FN BMD or no discordance.

Several factors are responsible for the development of spine–femur BMD discordance [6]. Weight bearing can increase bone density, particularly, in the hip and femur, which accounts for well-known physiological discordance [20]. This mechanism could explain the increased risk of major discordance in obese patients [7]. Furthermore, differences in the composition of the skeleton at the spine and femur may contribute to this discordance. Majority of LS is made up of the trabecular bone, while FN predominantly consists of the cortical bone. The trabecular bone, which accounts for 20% of the total bone mass, has an accelerated metabolism; therefore, the loss of bone exhibited is earlier and more rapid than that in the cortical bone [7]. Pathophysiological discordance, also known as secondary discordance, is associated with degenerative diseases, such as vertebral osteophytosis, vertebral endplate and facet sclerosis, osteochondrosis, and aortic calcification [21]. Anatomical discordance is due to differences in the bone envelope composition. Artifactual discordance occurs when dense manmade materials are within the region of interest of the test. Technical discordance occurs due to device errors, patients' movements, or technician variability.

The previously reported prevalence of spine–femur BMD discordance varied according to the definition of discordance and the study population of each study. A major discordance of more than two levels in the osteoporosis classification

Table 3 Comparison of biochemical parameters in subjects with and without spine–femur T-score discordance

(a) Men ($n = 3233$)

	Low LS ($n = 152$)	Without discordance ($n = 2816$)	Low FN ($n = 265$)	Adjusted P	P*
FPG (mg/dL)	101.9 ± 2.5	104.9 ± 0.6	110.6 ± 1.8	0.005	b, c
Insulin (mIU/L)	8.72 ± 0.46	9.58 ± 0.10	10.20 ± 0.34	0.035	b
HOMA-IR	2.16 ± 1.39	2.50 ± 1.61	3.08 ± 2.90	< 0.001	b, c
Total-C (mg/dL)	189.6 ± 3.3	187.1 ± 0.7	182.8 ± 2.4	0.162	
TG (mg/dL)	134.5 ± 11.4	160.9 ± 2.6	162.9 ± 8.4	0.073	
HDL-C (mg/dL)	50.7 ± 1.1	48.5 ± 0.3	47.4 ± 0.8	0.058	
LDL-C (mg/dL)	111.1 ± 3.4	105.9 ± 0.8	101.8 ± 2.5	0.089	
BUN (mg/dL)	15.6 ± 0.4	16.3 ± 0.1	16.8 ± 0.3	0.085	
Creatinine (mg/dL)	0.92 ± 0.12	0.95 ± 0.01	1.02 ± 0.01	< 0.001	b, c
25(OH) D (ng/mL)	21.9 ± 0.7	21.6 ± 0.1	21.3 ± 0.5	0.750	
PTH (pg/mL)	63.1 ± 2.3	65.0 ± 0.5	66.7 ± 1.7	0.422	

(b) Women ($n = 2915$)

	Low LS ($n = 159$)	Without discordance ($n = 2625$)	Low FN ($n = 131$)	Adjusted P	P*
FPG (mg/dL)	100.7 ± 2.1	102.3 ± 0.5	107.9 ± 2.4	0.048	
Insulin (mIU/L)	9.87 ± 0.48	10.43 ± 0.12	10.94 ± 0.52	0.315	
HOMA-IR	2.34 ± 1.16	2.72 ± 2.79	3.31 ± 2.63	0.020	b
Total-C (mg/dL)	202.1 ± 3.1	202.2 ± 0.8	208.1 ± 3.5	0.258	
TG (mg/dL)	125.2 ± 7.3	142.8 ± 1.8	148.3 ± 8.2	0.047	
HDL-C (mg/dL)	53.0 ± 1.1	51.6 ± 0.3	49.7 ± 1.2	0.103	
LDL-C (mg/dL)	123.2 ± 3.0	121.8 ± 0.8	128.0 ± 3.3	0.178	
BUN (mg/dL)	15.9 ± 0.4	15.6 ± 0.1	15.6 ± 0.4	0.692	
Creatinine (mg/dL)	0.69 ± 0.01	0.72 ± 0.01	0.80 ± 0.02	< 0.001	b, c
25(OH) D (ng/mL)	19.8 ± 0.6	18.4 ± 0.1	17.6 ± 0.6	0.027	b
PTH (pg/mL)	66.8 ± 2.8	67.9 ± 0.7	80.5 ± 3.2	0.001	b, c

Data are presented as mean ± SE or *n* (%). Adjusted *P* values are analyzed by ANCOVA after adjusting for age, BMI, WC, smoking status, drinking status, physical activity, daily calcium intake, and prevalent fracture

FPG fasting plasma glucose, *HOMA-IR* homeostasis model assessment of insulin resistance, *Total-C* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *BUN* blood urea nitrogen, *25(OH)D* 25-hydroxyvitamin D3, *PTH* parathyroid hormone

*Post hoc analysis using Bonferroni correction: a, $P < 0.05$ between low LS and without discordance; b, $P < 0.05$ between low LS and low FN; c, $P < 0.05$ between without discordance and low FN

was reported in 4.0–16.7% of subjects and a minor discordance in more than one level was reported in 34.5–42.0% of subjects [7, 22]. In the current study, we adopted the difference ≥ 1.5 SD as a level of the T-score discordance, to reflect the composite effects of major discordance and minor discordance.

We observed that subjects with low FN BMD presented higher FPG and HOMA-IR levels after adjusting for confounding factors, including age and BMI. In addition, the prevalence of metabolic diseases, including diabetes mellitus and hypertension, was higher in the low FN group. Our findings suggest a possible link between insulin resistance and cortical porosity in subjects with low FN BMD. In patients with altered glucose metabolism, such as type 2 diabetes, LS BMD is similar or may even be slightly higher than in those without type 2 diabetes; however, the actual fracture risk is increased in type 2 diabetes [23, 24]. Increased cortical porosity has been suggested as a possible factor responsible for bone fragility in type 2 diabetes [25, 26]. In the previous studies, using high-resolution peripheral quantitative computed tomography, lower cortical bone density and higher cortical porosity were observed in patients with type 2 diabetes [26–29]. The mechanism which could explain the association between cortical porosity and diabetes is not yet fully elucidated. However, several factors have been proposed as possible contributors to cortical porosity, including increased levels of advanced glycation end products (AGE) in the bone

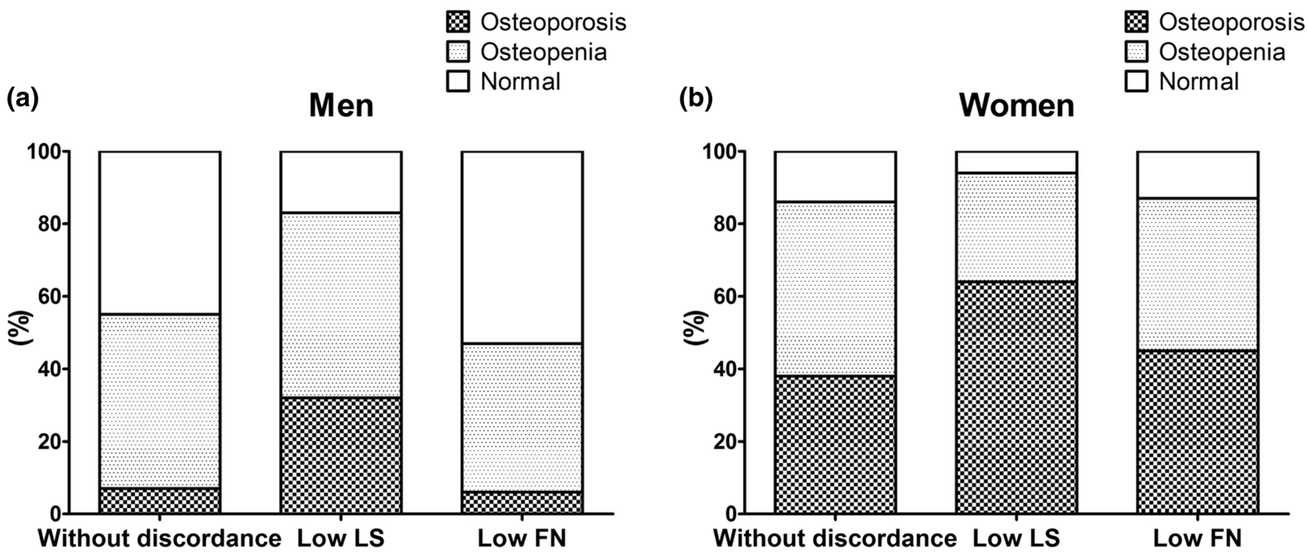

Fig. 2 Prevalence of osteoporosis according to the presence of spine–femur T-score discordance in **a** men and **b** women

matrix. A preliminary study reported a significant association between AGE pentosidine level and cortical porosity in type 2 diabetes [30]. In addition, the accumulation of AGEs may influence bone strength through bone matrix changes and lead to the development of oxidative stress and inflammatory responses [31].

As renal function decreases, serum PTH levels rise and, consequently, decrease BMD, particularly the cortical sites. Given the association of serum PTH levels and renal function, we have already excluded subjects with chronic renal failure from the analysis. We observed significantly higher serum creatinine and PTH levels in the low FN group than in the low LS group in women after adjusting for covariates including age and BMI. Similar trends were observed in men, however, not statistically significant. These results suggest that endogenous PTH could negatively affect BMD, especially FN BMD, in subjects who do not have clinically significant renal dysfunction.

In the previous studies, serum 25(OH)D level and calcium intake were negatively correlated with serum PTH concentration as well as FN BMD [32, 33]. Calcium intake revealed significantly inverse correlations with serum PTH level and FN BMD, particularly, in a low-25(OH)D population [34]. In the present study, we observed that low calcium intake was significantly associated with low FN group in men but not in women. Hence, we adjusted for dietary calcium intake as a confounding factor, to avoid its influence on 25(OH)D and serum PTH levels; the low FN group was significantly associated with low 25(OH) and high serum PTH concentration in women but not in men. The prevalence of fractures was not significantly different in subjects with and without discordance, and it did not differ between low LS and low FN BMD groups. This may be attributed to the limitation of fracture data, which could not solely include osteoporotic fractures.

Although LS BMD measurements are commonly performed in clinical practice for baseline risk assessment as well as monitoring treatment response, only FN BMD is currently incorporated in the WHO Fracture Risk Assessment Tool (FRAX®) [35]. This is partly because LS BMD is often elevated by spinal degenerative changes, such as ligamental calcification and osteophytes [36]. In addition, the previous studies did not reveal additional benefits with a combination of LS BMD and FN BMD for fracture prediction [37–39]. FN BMD is considered to be the best predictive value to predict the occurrence of major osteoporotic fractures, especially hip fractures [3]. However, if LS BMD is significantly lower than FN BMD, the probability of actual fracture occurrence may be higher than that calculated by FRAX® [39, 40]. Several studies have reported a 10–30% increase in fracture risk in patients with lower LS than FN T-score [41, 42]. Although no significant differences were observed in the prevalence of previous fractures according to the presence of discordance, we demonstrated significant associations between spine–femur BMD discordance and high prevalence of osteoporosis. These findings suggest that it is important to consider the occurrence of fragility fractures in patients with not only low BMD values but also BMD T-score discordances.

The present study has some limitations. We could not access the original DXA scans; therefore, spine levels with possible confounding pathology, including osteophyte formation, aortic calcification, osteoarthritis, or fracture, were not excluded from the analysis of LS BMD. Spinal degenerative changes, including osteophyte formation and ligamental calcification, increase with age. Considering the mean age of this study (65 years), a significant proportion of the study participants may have experienced degenerative changes in the spine. Indeed, subjects in the low FN group were older than those in the low LS or no discordance groups in both men and women. Further to this, assessment of a 10-year fracture risk probability using FRAX® was not available for the participants due to lack of data on clinical risk factors, including parental history of hip fracture and use of systemic glucocorticoids.

In conclusion, the current study provides valuable information on the significance of spine–femur BMD discordance from a metabolic standpoint. The spine–femur BMD T-score discordance was demonstrated in approximately 10% of the Korean population. Low FN BMD was significantly associated with insulin resistance, as well as low 25(OH)D and high serum PTH level. Notably, osteoporosis was more prevalent in subjects with spine–femur discordance, i.e., low LS BMD; these findings suggest the need for active surveillance for the occurrence of osteoporotic fractures in such populations. Considering the worldwide increase of the aging population and facilitated use of DXA in clinics, more attention should be paid to the appropriate evaluation and management of subjects with spine–femur BMD discordance.

Compliance with ethical standards

Conflict of interest A. Ram Hong, Jung Hee Kim, Ji Hyun Lee, Sang Wan Kim, and Chan Soo Shin declare that they have no conflicts of interest.

References

1. Kanis JA (2002) Diagnosis of osteoporosis and assessment of fracture risk. Lancet 359:1929–1936
2. Kanis JA, Gluer CC (2000) An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors, International Osteoporosis Foundation. Osteoporos Int 11:192–202
3. Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 312:1254–1259
4. Ahmed AI, Blake GM, Rymer JM, Fogelman I (1997) Screening for osteopenia and osteoporosis: do the accepted normal ranges lead to overdiagnosis? Osteoporos Int 7:432–438
5. Faulkner KG, von Stetten E, Miller P (1999) Discordance in patient classification using T-scores. J Clin Densitom 2:343–350
6. Woodson G (2000) Dual X-ray absorptiometry T-score concordance and discordance between the hip and spine measurement sites. J Clin Densitom 3:319–324
7. Mounach A, Abayi DA, Ghazi M, Ghozlani I, Nouijai A, Achemlal L, Bezza A, El Maghraoui A (2009) Discordance between hip and spine bone mineral density measurement using DXA: prevalence and risk factors. Semin Arthritis Rheum 38:467–471
8. Moayyeri A, Soltani A, Tabari NK, Sadatsafavi M, Hossein-Neghad A, Larijani B (2005) Discordance in diagnosis of osteoporosis using spine and hip bone densitometry. BMC Endocr Disord 5:3
9. Alarkawi D, Bliuc D, Nguyen TV, Eisman JA, Center JR (2016) Contribution of lumbar spine BMD to fracture risk in individuals with T-score discordance. J Bone Miner Res 31:274–280
10. Mulder JE, Michaeli D, Flaster ER, Siris E (2000) Comparison of bone mineral density of the phalanges, lumbar spine, hip, and forearm for the assessment of osteoporosis in postmenopausal women. J Clin Densitom 3:373–381
11. Abrahamsen B, Stilgren LS, Hermann AP, Tofteng CL, Barenholdt O, Vestergaard P, Brot C, Nielsen SP (2001) Discordance between changes in bone mineral density measured at different skeletal sites in perimenopausal women—implications for assessment of bone loss and response to therapy: the Danish Osteoporosis Prevention Study. J Bone Miner Res 16:1212–1219
12. El Maghraoui A, Mouinga Abayi DA, Ghozlani I, Mounach A, Nouijai A, Ghazi M, Achemlal L, Bezza A (2007) Prevalence and risk factors of discordance in diagnosis of osteoporosis using spine and hip bone densitometry. Ann Rheum Dis 66:271–272
13. Ahn SH, Lee SH, Kim H, Kim BJ, Koh JM (2014) Different relationships between body compositions and bone mineral density according to gender and age in Korean populations (KNHANES 2008–2010). J Clin Endocrinol Metab 99:3811–3820
14. Kim YJ, Jeon JY, Han SJ, Kim HJ, Lee KW, Kim DJ (2015) Effect of socio-economic status on the prevalence of diabetes. Yonsei Med J 56:641–647
15. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, Paffenbarger RS Jr (1993) Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 25:71–80
16. Schoeller DA, Tylavsky FA, Baer DJ et al (2005) QDR 4500A dual-energy X-ray absorptiometer underestimates fat mass in comparison with criterion methods in adults. Am J Clin Nutr 81:1018–1025
17. Kelly TL, Wilson KE, Heymsfield SB (2009) Dual energy X-Ray absorptiometry body composition reference values from NHANES. PLoS One 4:e7038
18. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499–502
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419
20. Kohrt WM, Snead DB, Slatopolsky E, Birge SJ Jr (1995) Additive effects of weight-bearing exercise and estrogen on bone mineral density in older women. J Bone Miner Res 10:1303–1311
21. Reid IR, Evans MC, Ames R, Wattie DJ (1991) The influence of osteophytes and aortic calcification on spinal mineral density in postmenopausal women. J Clin Endocrinol Metab 72:1372–1374
22. Singh M, Magon N, Singh T (2012) Major and minor discordance in the diagnosis of postmenopausal osteoporosis among Indian women using hip and spine dual-energy X-ray absorptiometry. J Midlife Health 3:76–80
23. Bonds DE, Larson JC, Schwartz AV, Strotmeyer ES, Robbins J, Rodriguez BL, Johnson KC, Margolis KL (2006) Risk of fracture in women with type 2 diabetes: the Women's Health Initiative Observational Study. J Clin Endocrinol Metab 91:3404–3410
24. Hanley DA, Brown JP, Tenenhouse A et al (2003) Associations among disease conditions, bone mineral density, and prevalent vertebral deformities in men and women 50 years of age and older: cross-sectional results from the Canadian Multicentre Osteoporosis Study. J Bone Miner Res 18:784–790
25. Paccou J, Ward KA, Jameson KA, Dennison EM, Cooper C, Edwards MH (2016) Bone microarchitecture in men and women

with diabetes: the importance of cortical porosity. Calcif Tissue Int 98:465–473
26. Yu EW, Putman MS, Derrico N, Abrishamanian-Garcia G, Finkelstein JS, Bouxsein ML (2015) Defects in cortical microarchitecture among African-American women with type 2 diabetes. Osteoporos Int 26:673–679
27. Burghardt AJ, Issever AS, Schwartz AV, Davis KA, Masharani U, Majumdar S, Link TM (2010) High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 95:5045–5055
28. Patsch JM, Burghardt AJ, Yap SP, Baum T, Schwartz AV, Joseph GB, Link TM (2013) Increased cortical porosity in type 2 diabetic postmenopausal women with fragility fractures. J Bone Miner Res 28:313–324
29. Samelson EJ, Demissie S, Cupples LA et al (2017) Diabetes and deficits in cortical bone density, microarchitecture, and bone size: Framingham HR-pQCT Study. J Bone Miner Res 33:54–62
30. Fink DFJ, Zhang C, Anderson LB, Jiang H, Cremers S, Nishiyama K, Zhou H, Dempster D, Poundarik A, Silverberg S, Vashishth D, Rubin M (2014) Bone properties in type 2 diabetes are associated with the advanced glycation end product pentosidine. J Bone Miner Res 29(Suppl 1):S116–S117
31. Yamagishi S (2011) Role of advanced glycation end products (AGEs) in osteoporosis in diabetes. Curr Drug Targets 12:2096–2102
32. Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G (2005) Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. JAMA 294:2336–2341
33. Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, Orav JE, Li R, Spiegelman D, Dietrich T, Willett WC (2009) Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among US adults. J Bone Miner Res 24:935–942
34. Joo NS, Dawson-Hughes B, Kim YS, Oh K, Yeum KJ (2013) Impact of calcium and vitamin D insufficiencies on serum parathyroid hormone and bone mineral density: analysis of the fourth and fifth Korea National Health and Nutrition Examination Survey (KNHANES IV-3, 2009 and KNHANES V-1, 2010). J Bone Miner Res 28:764–770
35. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E (2008) FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 19:385–397
36. Tenne M, McGuigan F, Besjakov J, Gerdhem P, Akesson K (2013) Degenerative changes at the lumbar spine—implications for bone mineral density measurement in elderly women. Osteoporos Int 24:1419–1428
37. Kanis JA, Johnell O, Oden A, Johansson H, Eisman JA, Fujiwara S, Kroger H, Honkanen R, Melton LJ 3rd, O'Neill T, Reeve J, Silman A, Tenenhouse A (2006) The use of multiple sites for the diagnosis of osteoporosis. Osteoporos Int 17:527–534
38. Leslie WD, Lix LM, Tsang JF, Caetano PA (2007) Single-site vs multisite bone density measurement for fracture prediction. Arch Intern Med 167:1641–1647
39. Leslie WD, Lix LM (2011) Absolute fracture risk assessment using lumbar spine and femoral neck bone density measurements: derivation and validation of a hybrid system. J Bone Miner Res 26:460–467
40. Leslie WD, Kovacs CS, Olszynski WP, Towheed T, Kaiser SM, Prior JC, Josse RG, Jamal SA, Kreiger N, Goltzman D (2011) Spine–hip T-score difference predicts major osteoporotic fracture risk independent of FRAX((R)): a population-based report from CAMOS. J Clin Densitom 14:286–293
41. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA (2011) Spine–hip discordance and fracture risk assessment: a physician-friendly FRAX enhancement. Osteoporos Int 22:839–847
42. Blackburn TD, Howard DB, Leib ES (2013) Utility of spine bone mineral density in fracture prediction within FRAX. J Clin Densitom 16:81–86