The Association of Vitamin D With Femoral Neck Strength: An Additional Evidence of Vitamin D on Bone Health

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Context: Although bone mineral density (BMD) is a strong predictor of fracture risk, additional parameters, such as bone strength, are needed to predict future fracture risk because of the low sensitivity of BMD for predicting fracture risk.

Objective: The objective was to study the association of vitamin D with femoral neck (FN) strength.

Design and Setting: This was a population-based, cross-sectional study from Korea National Health and Nutrition Examination Surveys.

Participants: A total of 1209 Koreans (586 men and 623 women) aged ≥50 years participated.

Main Outcome Measures: We calculated composite indices of FN strength, such as the compression strength index, bending strength index (BSI), and impact strength index, by combining BMD, body weight, and height with the femoral axis length and width, which were measured by dual-energy x-ray absorptiometry.

Results: Multiple regression analysis demonstrated that serum 25-hydroxyvitamin D [25(OH)D] levels were associated with compression strength index, BSI, and impact strength index in both genders. When women were categorized into four quartiles of 25(OH)D, FN BMD and composite indices (except for BSI) significantly increased from the lowest (Q1) to the highest quartile (Q4) (*P* for trend = .001–.004). In contrast, there is no significant association of quartiles with composite indices in men. When women were divided into two groups according to their serum 25(OH)D levels, the composite indices as well as the FN BMD were markedly higher in subjects with higher 25(OH)D levels (≥51.5 nmol/L).

Conclusion: These findings provide the first clinical evidence that high serum 25(OH)D levels exhibit higher composite indices of FN strength in a dose-dependent manner, especially in women. (***J Clin Endocrinol Metab*** **100: 3118–3125, 2015)**

As the incidence and prevalence of osteoporosis greatly increased, osteoporotic fracture (OF) has become a very serious, worldwide, public health problem (1, 2). Among all types of OF, hip fracture is the most serious because of the high morbidity and mortality (3). Bone mineral density (BMD) is a strong predictor of fracture risk; however, an additional parameter such as bone strength is required to predict future fracture risk due to the low sensitivity of BMD for predicting fracture risk (4). Several previous studies reported that an increase in bone size is a partially compensatory mechanism for age-related BMD loss (5) and that body size determines the fracture

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Abbreviations: ANCOVA, analysis of covariance; BMD, bone mineral density; BSI, bending strength index; CI, confidence interval; CSI, compression strength index; DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; FN, femoral neck; FNW, FN width; HAL, hip axis length; HSA, hip-structure analysis; ISI, impact strength index; OF, osteoporotic fracture; 25(OH)D, 25-hydroxyvitamin D; Q, quartile; WC, waist circumference.

forces during a fall (6). These factors suggest that body size and femoral neck (FN) geometry contribute to predicting fracture risk, independent of the BMD. Karlamangla et al (7) developed the concept of composite indices of FN strength. These indices are composed of FN BMD, FN geometry, and body size to determine the structural contributions to bone strength (resistance to fracture forces) relative to load (forces placed on the hip during a fall). These indices are inversely associated with the incidental hip fracture risk in Caucasian and Chinese adults (8, 9).

Vitamin D has an essential role in bone and mineral metabolism. Higher 25(OH)D levels have also been associated with higher BMD (10), and vitamin D supplementation also reduces bone loss rates (11). Recently, several studies have shown that high 25(OH)D levels and vitamin D supplementation may improve the hip geometry, including the cross-sectional area, cross-sectional moment of inertia, and cortical thickness (12, 13). Therefore, we could hypothesize that the skeletal changes seen in patients with high 25(OH)D levels may at least partially contribute to the improvement in FN strength. We aimed to evaluate the associations of serum 25(OH)D levels with the composite indices of FN strength in a representative community cohort in South Korea.

Subjects and Methods

Study subjects

This cross-sectional study was based on data acquired in the Fourth Korean National Health and Nutrition Examination Survey (KNHANES IV), which was conducted from 2007 to 2009. The KNHANES is a cross-sectional, nationwide survey performed by the Division of Chronic Disease Surveillance, Korea Centers for Disease Control and Prevention. This nationwide survey used a stratified, multistage, clustered probability sampling method to select a representative sample of the noninstitutionalized, civilian Korean population. The survey consisted of a health interview survey, a nutrition survey, and a health examination survey. All participants in the KNHANES survey provided informed consent. The database of KNHANES is publicly available at the KNHANES web site (http://knhanes.cdc.go.kr/knhanes/eng; available in English).

A total of 4594, 9744, and 10 533 subjects participated in KNHANES IV in 2007, 2008, and 2009, respectively. The response rates were 71.2, 77.8, and 82.8%, respectively. Serum concentration of 25(OH)D and information regarding hip geometry and BMD were available for 1632 KNHANES subjects (677 men and 955 women) who were age 50 or older. Individuals with a history of any neoplastic disease, increased serum liver enzyme activity (aspartate aminotransferase or alanine aminotransferase >100 IU/L), decreased renal function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), and/or who had taken drugs that could affect bone metabolism, such as bisphosphonate or hormone replacement therapy (n = 423), were excluded. The remaining 1209 subjects (586 men and 623 women) were eligible for inclusion.

Measurements of clinical and laboratory parameters

Information regarding age, height, body weight, waist circumference (WC), smoking, drinking and exercise habits, and calcium and phosphorus intake was collected from all study subjects. Smoking habit was categorized into three levels, ie, never, past, or current. Drinking habit was indicated as "yes" when the subject drank ≥ three units of alcohol per day. The exercise group was defined as subjects who exercised ≥20 minutes per session and ≥3 d/wk. Dietary intake of calcium and phosphorus was calculated using the 24-hour dietary recall method. Anthropometric factors such as height (centimeters) and body weight (kilograms) were measured using standardized protocols while the subject was dressed in light clothing and without shoes. WC (centimeters) was measured between the lower rib margin and the iliac crest at the end of a normal expiration. Body mass index (BMI) (kg/m^2) was calculated according to the subject's height and weight. Diabetes mellitus was diagnosed with the criteria revised in 2003 by the American Diabetes Association (14) and using the history of antidiabetic medication (eg, insulin or oral agents).

After overnight fasting for ≥8 hours, blood samples were drawn from all participants during the survey, immediately refrigerated, and then transported to the Central Testing Institute (Neodin Medical Institute). All blood samples were analyzed within 24 hours after transport. Serum 25(OH)D concentrations were measured by competitive RIA (DiaSorin) using a γ-counter (1470 Wizard; PerkinElmer; reference range, 75–250 nmol/L). Serum creatinine concentration was measured colorimetrically using a Hitachi Automatic Analyzer 7600 (Hitachi; reference ranges, 53–106 μmol/L for men, 44–80 μmol/L for women). eGFR was calculated using the Modification of Diet in Renal Disease study formula: eGFR (mL/min/1.73 m^2) = [186 × serum creatinine (mg/dL)$^{-1.154}$] × age$^{-0.203}$ (×0.742 if female) (15).

BMD measurements

In the KNHANES, BMD at the lumbar spine, FN, and total femur was measured using dual-energy x-ray absorptiometry (DXA; QDR 4500A; Hologic Inc) at mobile examination centers operated by licensed, trained technicians. Reference values of DXA instruments were obtained using this calibration method (16). We maintained DXA calibration via an internal referencing system and daily measured spine phantoms supplied by the manufacturers, which are bone and soft-tissue-equivalent reference standards (17, 18). The in vivo precision at FN was less than 2.5%. These values were obtained by scanning 30 randomly selected subjects who underwent two scans on the same day while getting off and back onto the examination table between their examinations. BMD values were compared with those of healthy young Japanese adults (T-score), which were provided by the equipment manufacturer (19). Osteoporosis was defined by a T-score ≤ −2.5 SD at any of the sites in the lumbar spine, FN, or total femur (20).

The bone-geometry structural properties were measured by DXA and were further analyzed using the hip-structure analysis (HSA) program that was included in the APEX software of Hologic (21). The HSA program automatically set the region of interest, defined as the narrow neck, as transversing the narrowest FN width (FNW). The coefficient of variance of the HSA indices, which were calculated from the same images used for the precision assessment of BMD, was approximately 2%.

Table 1. Baseline Characteristics of the Study Population

Characteristic	Women	Men	*P* Value
n	623	586	
Age, y	58.5 (57.3–59.6)	56.6 (55.6–57.6)	.059
Height, cm	154.3 (153.7–154.9)	167.5 (166.9–168.0)	<.001
Weight, kg	56.6 (55.8–57.5)	67.3 (66.4–68.3)	<.001
BMI, kg/m^2	23.8 (23.5–24.1)	24.0 (23.7–24.3)	.203
eGFR, mL/min/1.73 m^2	72.1 (69.1–82.4)	79.0 (76.6–81.3)	<.001
Alcohol drinker, n (%)	34 (5.5)	256 (43.7)	<.001
Current smoker, n (%)	44 (7.1)	234 (39.9)	<.001
Regular exercise, n (%)	109 (17.5)	101 (17.2)	.609
Calcium intake, mg/d	412.8 (377.9–447.7)	514.5 (481.5–547.6)	<.001
Phosphorus intake, mg/d	951.9 (903.4–1000.4)	1277.5 (1228.4–1326.5)	<.001
25(OH)D, nmol/L	51.8 (49.7–53.9)	61.0 (58.7–63.2)	<.001
Osteoporosis prevalence, n (%)	249 (39.9)	34 (5.8)	<.001
FN BMD, g/cm^2	0.653 (0.640–0.665)	0.779 (0.767–0.790)	<.001
CSI, g/kg · m	3.73 (3.66–3.79)	4.25 (4.18–4.32)	<.001
BSI, g/kg · m	1.19 (1.17–1.21)	1.37 (1.35–1.40)	<.001
ISI, g/kg · m	0.243 (0.239–0.247)	0.286 (0.281–0.291)	<.001

Values are presented as mean (95% CI) unless otherwise specified. *P* values were determined using the Student's *t* test for continuous variables and the χ^2 test for categorical variables.

Composite indices of FN strength

The compression strength index (CSI), bending strength index (BSI), and impact strength index (ISI) at the FN were measured from the mean FNW and hip axis length (HAL), together with the height, weight, and FN BMD for evaluating the capacity of the FN to endure the load during a fall. The FNW is the least FN thickness along any line perpendicular to the FN axis. The HAL reflects the distance along the FN axis from the lateral margin at the base of the greater trochanter to the inner pelvic brim. Equations for the composite indices, previously described by Karlamangla et al (7), are as follows: CSI = (BMD × FNW)/weight; BSI = (BMD × FNW^2)/(HAL × weight); and ISI = (BMD × FNW × HAL)/(height × weight).

CSI reflects the FN ability to withstand an axial compressive load, BSI reflects the FN ability to withstand bending forces, and ISI reflects the FN ability to absorb the energy of impact in a fall from the standing height.

Statistical analysis

All data are presented as means with 95% confidence intervals (CIs), or as numbers and percentages, unless otherwise specified. The baseline characteristics were calculated using an unpaired *t* test for continuous variables or the χ^2 test for categorical variables. To test our hypothesis that higher 25(OH)D concentrations might be associated with higher FN BMD and indices of FN strength, we performed multiple regression analysis before and after adjustment. We used two adjustment models; one was the base model, and the other was the multivariable model. The base adjustment model included age, height, weight, and WC, whereas the multivariable model included age, height, weight, WC, eGFR, alcohol status, smoking status, exercise status, calcium intake, and phosphorus intake. These confounding variables were selected on the basis of being clinically applicable. We categorized subjects into four groups according to their serum 25(OH)D concentrations and then performed analysis of covariance (ANCOVA) and compared the estimated means of FN BMD and the composite indices according to their 25(OH)D quartiles. The trend of FN BMD and the composite indices across increasing quartiles of 25(OH)D were checked by examining *P* values for the trends using multiple, linear-regression analysis. Multivariate-adjusted, least-square means with 95% CIs of FN BMD and composite indices in subjects with high or low serum 25(OH)D were estimated and compared by ANCOVA before and after adjustment. All analyses were performed while considering sample weighting using the Complex Samples Plan (CSPLAN) which is available as the Complex Samples option in the high SPSS version (SPSS Inc). In the present study, SPSS statistical software version 18.0 was used, and $P < .05$ was considered to indicate statistical significance.

Results

Clinical characteristics of the study subjects

The baseline characteristics of the subjects are presented in Table 1. Among the subjects, 623 (51.8%) were women, and 586 (48.2%) were men. The mean age of the women was 58.5 years (95% CI = 57.3–59.6 y; range, 50–89 y), and the mean age of the men was 56.6 years (95% CI = 55.6–57.6 y; range, 50–86 y). Men had greater height, weight, BMI, eGFR, calcium intake, phosphorus intake, FN BMD, and all composite indices than did the women. The osteoporosis prevalence of the men and women was 5.8 and 39.9%, respectively. The KNHANES uses a stratified, multistage, clustered probability sampling method to select a representative sample of the noninstitutionalized, civilian Korean population. We analyzed the prevalence of osteoporosis while considering the sample weighting. Thus, these analytical methods could rightly analyze the prevalence of osteoporosis in women over 50 years of age. The prevalence was similar to those in other studies (22, 23). Regular exercise was

Table 2. Multiple Regression Analysis Performed to Determine Whether Serum 25(OH)D Concentrations Associate Independently With FN BMD and Composite Indices of FN Strength

	25(OH)D, nmol/L								
	Unadjusted			Base Model			Multivariable Model		
Dependent Variables	β	SE	*P* Value[a]	β	SE	*P* Value	β	SE	*P* Value
Women									
FN BMD, g/cm^2	**0.001**	**0.000**	**.036**	**0.002**	**0.001**	**.002**	**0.002**	**0.001**	**.001**
CSI, g/kg · m	0.003	0.002	.100	**0.009**	**0.003**	**.002**	**0.010**	**0.003**	**.001**
BSI, g/kg · m	0.001	0.001	.249	0.001	0.001	.071	**0.002**	**0.001**	**.047**
ISI, g/kg · m	0.001	0.000	.063	**0.001**	**0.000**	**.003**	**0.001**	**0.000**	**<.001**
Men									
FN BMD, g/cm^2	−0.001	0.001	.356	0.000	0.001	.515	0.000	0.001	.950
CSI, g/kg · m	**0.011**	**0.004**	**.010**	**0.007**	**0.003**	**.028**	0.005	0.004	.076
BSI, g/kg · m	**0.004**	**0.001**	**.007**	**0.003**	**0.001**	**.019**	**0.003**	**0.001**	**.032**
ISI, g/kg · m	**0.001**	**0.000**	**.002**	**0.001**	**0.000**	**.008**	**0.001**	**0.000**	**.027**

Base model is adjusted for age, height, weight, and WC. Multivariable model is adjusted for age, height, weight, WC, eGFR, alcohol status (≥3 U/d), smoking status, exercise status (≥30 min/d), calcium intake, and phosphorus intake. Boldface data indicate that the differences were statistically significant.

[a] *P* values were generated using a simple regression analysis.

higher in women than in men, whereas the percentage of alcohol drinkers and current smokers was lower in women than in men. The mean serum 25(OH)D level was 51.8 (95% CI = 49.7–53.9) nmol/L in women and 61.0 (95% CI = 58.7–63.2) nmol/L in men.

Association between serum 25(OH)D levels with FN BMD and composite indices of FN strength

We performed multiple regression analysis to determine whether the 25(OH)D levels were independently associated with FN BMD and the composite indices of FN strength (Table 2). In all models, 25(OH)D levels were significantly associated with FN BMD in women, but not in men. Before adjustment, there was no significant association between 25(OH)D levels with composite indices in women. After adjusting for age, height, weight, and WC in women, 25(OH)D was significantly or marginally correlated with composite indices. Even after adjustment for all potential confounders, 25(OH)D levels were significantly associated with all composite indices. In men, 25(OH)D levels showed a significant association with composite indices before and after adjusting for confounders, except for CSI with marginal significance on the multivariable model. The number of subjects with and without diabetes was 517 and 106 in women and 497 and 89 in men, respectively. An additional adjustment for the status of diabetes did not generally affect the associations (Supplemental Table 1). This suggests that the noted associations were independent from diabetes. In

Table 3. Multiple Regression Analysis Performed to Determine Whether Serum 25(OH)D Concentrations Associate Independently With FN BMD and Composite Indices of FN Strength According to Their Age

	25(OH)D, nmol/L											
	Age 50–64 y (n = 394 Women, 396 Men)						Age ≥65 y (n = 229 Women, 190 Men)					
	Unadjusted			Multivariable Model			Unadjusted			Multivariable Model		
Dependent Variables	β	SE	*P* Value[a]	β	SE	*P* Value	β	SE	*P* Value[a]	β	SE	*P* Value
Women												
FN BMD, g/cm^2	0.001	0.001	.292	0.001	0.000	.067	**0.002**	**0.001**	**.004**	**0.002**	**0.001**	**.001**
CSI, g/kg · m	0.005	0.003	.070	**0.007**	**0.002**	**.004**	**0.011**	**0.005**	**.020**	**0.013**	**0.003**	**.002**
BSI, g/kg · m	0.001	0.001	.512	**0.002**	**0.001**	**.027**	0.003	0.002	.139	**0.003**	**0.002**	**.049**
ISI, g/kg · m	0.000	0.000	.240	**0.001**	**0.000**	**.009**	**0.001**	**0.000**	**.018**	**0.001**	**0.000**	**.001**
Men												
FN BMD, g/cm^2	0.001	0.001	.510	0.000	0.001	.683	0.000	0.001	.749	0.002	0.001	.205
CSI, g/kg · m	0.006	0.005	.225	0.005	0.003	.194	**0.031**	**0.007**	**<.001**	0.012	0.008	.123
BSI, g/kg · m	0.003	0.002	.108	0.002	0.001	.071	**0.009**	**0.003**	**.001**	0.004	0.003	.130
ISI, g/kg · m	0.001	0.000	.130	0.000	0.000	.106	**0.002**	**0.001**	**<.001**	**0.001**	**0.000**	**.049**

Base model is adjusted for age, height, weight, and WC. Multivariable model is adjusted for age, height, weight, WC, eGFR, alcohol status (≥3 U/d), smoking status, exercise status (≥30 min/d), calcium intake, and phosphorus intake. Boldface data indicate that the differences were statistically significant.

[a] *P* values were generated using a simple regression analysis.

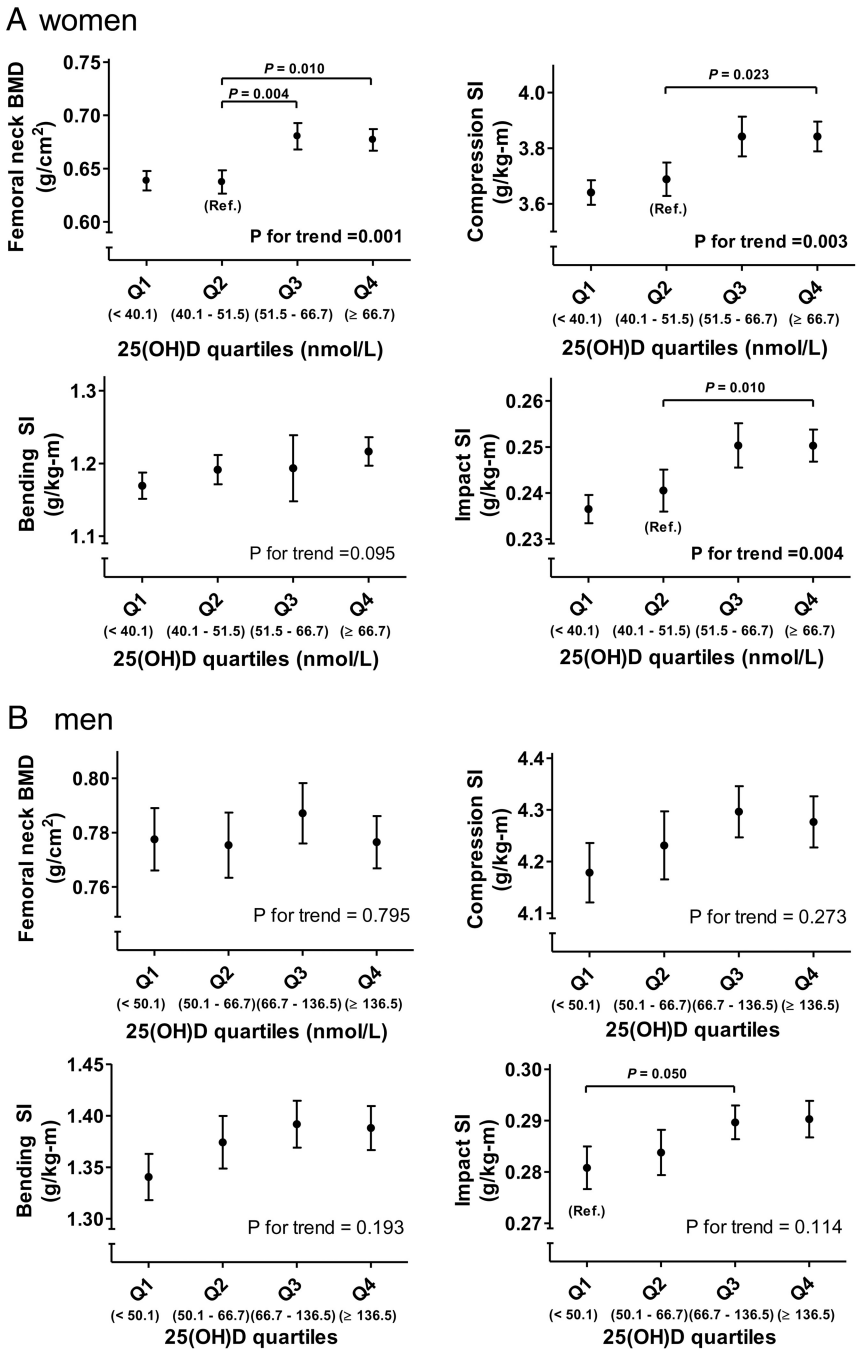

Figure 1. Levels of FN BMD, CSI, BSI, and ISI after adjustment for confounding variables according to the quartiles of serum 25(OH)D in women (A) and men (B). Values are presented as the estimated mean with 95% CIs after adjustment for confounding variables using ANCOVA. Bold font indicates that the differences were statistically significant. Confounding variables include age, height, weight, WC, eGFR, alcohol status (≥3 U/d), smoking status, exercise status (≥30 min/d), calcium intake, and phosphorus intake.

addition, we divided our subjects into middle-aged (50–64 y) and older (≥65 y) subgroups (Table 3). In women of both subgroups, 25(OH)D levels were significantly associated with all composite indices, after adjustment for all confounders (P = .001–.049). However, some composite indices showed significant or marginal associations with 25(OH)D only in older men, not in middle-aged men.

FN BMD and composite indices of FN strength, depending on the quartiles of serum 25(OH)D levels

When subjects were categorized into four quartiles (Figure 1), FN BMD and composite indices (except for BSI) significantly increased from the lowest quartile (Q1) to the highest quartile (Q4) in women after adjustment for all confounders (P for trend = .001–.004). In contrast, the associations of the quartiles with FN BMD and the composite indices were insignificant in men.

Differences in FN BMD and the composite indices of FN before and after adjustment for confounders according to the serum 25(OH)D levels

In women, CSI and ISI in the Q3 (range, 51.5–66.7 nmol/L) were marginally increased (P = .075 and .098, respectively), and those in the Q4 (range, 66.7–136.5 nmol/L) were significantly increased (P = .023 and .010, respectively) compared with subjects in the Q2 (range, 40.1–51.5 nmol/L), whereas they were similar in the Q1 (range, 11.2–40.1 nmol/L) compared with the Q2. Therefore, we performed exploratory subanalyses using the cutoff value of serum 25(OH)D (51.5 nmol/L) that showed the differences in women. The women with high 25(OH)D had consistently higher FN BMD and composite indices than subjects with low 25(OH)D, after adjustment for age, height, weight, and WC (Table 4). Even after adjustment for all potential confounders, the subjects with serum 25(OH)D of 51.5 nmol/L or higher still had a higher FN BMD and composite indices.

In addition, we investigated differences in FNW or HAL according to the serum 25(OH)D levels (Supplemental Table 2). There were no significant differences of HAL in both genders according to the serum 25(OH)D levels. However, there was the marginal difference of FNW according to the serum 25(OH)D levels in men (P = .065), but not in women.

Table 4. FN BMD and Composite Indices of FN Strength Relative to Serum 25(OH)D Levels in Women

	Unadjusted			Base Model			Multivariable Model		
	Estimated Mean (95% CI)			Estimated Mean (95% CI)			Estimated Mean (95% CI)		
	25(OH)D < 51.5 nmol/L	25(OH)D ≥ 51.5 nmol/L	*P* Value	25(OH)D < 51.5 nmol/L	25(OH)D ≥ 51.5 nmol/L	*P* Value	25(OH)D < 51.5 nmol/L	25(OH)D ≥ 51.5 nmol/L	*P* Value
FN BMD, g/cm^2	**0.642 (0.626–0.658)**	**0.674 (0.653–0.694)**	**.016**	**0.639 (0.627–0.652)**	**0.677 (0.663–0.691)**	**<.001**	**0.638 (0.626–0.650)**	**0.679 (0.665–0.693)**	**<.001**
CSI, g/kg · m	3.69 (3.60–3.77)	3.81 (3.71–3.91)	.068	**3.66 (3.60–3.73)**	**3.84 (3.76–3.91)**	**.001**	**3.66 (3.60–3.73)**	**3.84 (3.77–3.92)**	**.001**
BSI, g/kg · m	1.19 (1.16–1.21)	1.21 (1.18–1.25)	.214	**1.18 (1.16–1.21)**	**1.22 (1.19–1.25)**	**.047**	**1.18 (1.16–1.20)**	**1.22 (1.19–1.25)**	**.025**
ISI, g/kg · m	**0.240 (0.234–0.245)**	**0.248 (0.242–0.255)**	**.046**	**0.238 (0.234–0.243)**	**0.250 (0.245–0.255)**	**.001**	**0.238 (0.234–0.243)**	**0.250 (0.245–0.255)**	**.001**

Estimated mean (95% CI) before and after adjustment for confounding variables was generated and compared using ANCOVA. Base model is adjusted for age, height, weight, and WC. Multivariable model is adjusted for age, height, weight, WC, eGFR, alcohol status (≥3 U/d), smoking status, exercise status (≥30 min/d), calcium intake, and phosphorus intake. Boldface data indicate that the differences were statistically significant.

Discussion

We showed that Korean women with higher 25(OH)D levels had significantly higher FN BMD and composite indices of FN strength than women with low 25(OH)D levels. In men, higher 25(OH)D levels were significantly associated with higher BSI and ISI, although the association between 25(OH)D with CSI showed only a marginal significance. Furthermore, FN BMD and composite indices increased in a dose-dependent manner across increasing 25(OH)D levels in women after adjustment for potential confounders. To our knowledge, this is the first study to show that vitamin D is associated with composite indices of FN strength, especially in middle-aged and older adults (24).

Composite indices of the FN strength combine the FN BMD and size with body size to estimate the bone strength relative to the load (impact forces) during a fall (7). These composite indices designed to quantify bone strength in the FN have the advantage of ease of measurement through DXA. These indices can help to increase the fracture risk prediction in diabetic patients as well as in the general population, compared to BMD alone (7). For example, despite having a high BMD, diabetic patients usually have a high incidence of FN fracture compared to the general population (25). The increased fracture risk in subjects with diabetes is consistent with the lower composite indices seen in persons with diabetes relative to nondiabetics (26).

Besides the effect of 25(OH)D levels on FN BMD, a recent study using KNHANES data similar to our study population showed that high 25(OH)D levels were associated with other parameters of hip geometry, such as higher cortical thickness, cross-sectional area, and cross-sectional moment of inertia, and lesser buckling ratio (27). Consistent with the recent study (27), our study showed the trend to higher FNW as a parameter of hip geometry in men with high 25(OH)D levels, but not in women. Therefore, we supposed that the association between 25(OH)D and composite indices might be mainly mediated by effects of 25(OH)D on FN BMD and might be partially mediated by effects of 25(OH)D on hip geometry.

Several randomized controlled studies verified that vitamin D supplementation may reduce the risk of hip fracture. First, higher 25(OH)D levels were associated with improved lower extremity function and physical performance (28, 29) by improving muscle strength. Second, higher 25(OH)D levels appear to have a favorable effect on postural balance in older adults (30). Third, vitamin D supplementation may increase BMD, resulting in the reduction of fracture risk. Fourth, high 25(OH)D levels and vitamin D supplementation may improve bone strength via effects on hip geometry, including the cross-sectional area, cross-sectional moment of inertia, and the cortical thickness and volume (31, 32). Finally, our study added another suggestion that one of the beneficial effects of vitamin D on antifracture efficacy may originate from the maintenance of composite indices of FN strength.

Our results suggest that the maintenance of appropriate serum 25(OH)D levels may also be important in maintaining FN strength. We also show that, although there was only a statistical significance in women, maintaining serum 25(OH)D levels >50 nmol/L is important. In line with our results, one prospective, nested, case-control study showed that women with the lowest 25(OH)D concentrations (<47.6 nmol/L) at study entry had a significantly greater risk for subsequent hip fracture during the 7 years (adjusted odds ratio = 1.71; 95% CI = 1.05–2.79) (33). Recently, the Institute of Medicine of the US National Academy of Sciences also recommended that a 25(OH)D level of 50 nmol/L (20 ng/dL) is necessary for maintaining the general level of public health (34). Therefore, for maintaining appropriate serum 25(OH)D levels, sufficient vitamin D supplementation is necessary for improving bone strength and decreasing fracture risk.

In our study, the associations of higher 25(OH)D levels with higher bone strength were more dominant in women than in men. These differences by gender are thought to be due to the rapid changes of sex hormones in women 50 years of age or older, as well as the other gender differences. No associations between 25(OH)D levels and composite indices in middle-aged men (ages 50–64 y) additionally implicate this possibility because sex hormone alterations are less significant in middle-aged men than women (35). Many studies showed that estrogen has an important role in bone metabolism (36). In women, the decline in estrogen and/or the increase in gonadotropins during menopause results in a reversal of bone remodeling such that resorption now exceeds formation and bone mass decreases, and coincident with this is the modeling-induced disruption of the bone microarchitecture. Recent studies have also suggested that changes of sex steroids (37), primarily estrogen and T, may have an influence on hip geometry. Therefore, our current results indicate that middle-aged adults, especially women undergoing this dynamic period of menopause that causes enormous changes in bone metabolism, may be more vulnerable to vitamin D deficiency and the subsequent mechanical and biochemical changes. However, we cannot show more direct evidence on the role of sex hormones in the association between vitamin D and bone strength indices because neither sex hormone levels nor menopausal stages were investigated in this study.

The major strength of our study is that it is a large population-based study using well-collected national data, which enhances the statistical reliability of the results and the generalizability of the data. Our study also has several limitations. First, because it was cross-sectional in design, the observed associations between 25(OH)D and the composite indices may not indicate a cause-and-effect relationship. Second, because serum concentrations of calcium, phosphate, and PTH were not measured in the survey, we could not exclude subjects with mineral metabolism disorders such as primary hyperparathyroidism. However, inclusion of these subjects would have been unlikely to substantially affect our study results because these disorders are not prevalent in the general population. Lastly, the composite indices in our study are based on macroscopic measurements from DXA scans; they do not reflect microscopic features such as the quality of cancellous mineralization and the microarchitecture, which can be measured by quantitative computed tomography, both of which are important determinants of bone strength.

In conclusion, we found that subjects with high 25(OH)D levels exhibited higher composite indices of FN strength in middle-aged and older adults, regardless of gender differences. The important clinical implication of our study is that subjects with high 25(OH)D levels or vitamin D supplementation may have a reduced OF risk due to their increased bone strength.

Acknowledgments

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References

1. **Reginster JY, Burlet N.** Osteoporosis: a still increasing prevalence. *Bone*. 2006;38:S4–S9.
2. **Park C, Ha YC, Jang S, Jang S, Yoon HK, Lee YK.** The incidence and residual lifetime risk of osteoporosis-related fractures in Korea. *J Bone Miner Metab*. 2011;29:744–751.
3. **Mayhew PM, Thomas CD, Clement JG, et al.** Relation between age, femoral neck cortical stability, and hip fracture risk. *Lancet*. 2005; 366:129–135.
4. **Siris ES, Chen YT, Abbott TA, et al.** Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med*. 2004;164:1108–1112.
5. **Heaney RP, Barger-Lux MJ, Davies KM, Ryan RA, Johnson ML, Gong G.** Bone dimensional change with age: interactions of genetic, hormonal, and body size variables. *Osteoporos Int*. 1997;7:426–431.
6. **Beck TJ, Petit MA, Wu G, LeBoff MS, Cauley JA, Chen Z.** Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the Women's Health Initiative-observational study. *J Bone Miner Res*. 2009;24:1369–1379.
7. **Karlamangla AS, Barrett-Connor E, Young J, Greendale GA.** Hip fracture risk assessment using composite indices of femoral neck strength: the Rancho Bernardo study. *Osteoporos Int*. 2004;15: 62–70.
8. **Ishii S, Greendale GA, Cauley JA, et al.** Fracture risk assessment without race/ethnicity information. *J Clin Endocrinol Metab*. 2012; 97:3593–3602.
9. **Yu N, Liu YJ, Pei Y, et al.** Evaluation of compressive strength index of the femoral neck in Caucasians and Chinese. *Calcif Tissue Int*. 2010;87:324–332.
10. **Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, et al.** Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. *J Bone Miner Res*. 2009;24:935–942.
11. **Ooms ME, Roos JC, Bezemer PD, van der Vijgh WJ, Bouter LM, Lips P.** Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial. *J Clin Endocrinol Metab*. 1995;80:1052–1058.
12. **Ito M, Nakamura T, Fukunaga M, Shiraki M, Matsumoto T.** Effect of eldecalcitol, an active vitamin D analog, on hip structure and biomechanical properties: 3D assessment by clinical CT. *Bone*. 2011;49:328–334.
13. **Lee YH, Kim JE, Roh YH, et al.** The combination of vitamin D

deficiency and mild to moderate chronic kidney disease is associated with low bone mineral density and deteriorated femoral microarchitecture: results from the KNHANES 2008–2011. *J Clin Endocrinol Metab*. 2014;99:3879–3888.
14. **American Diabetes Association.** Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2012;35(suppl 1):S64–S71.
15. **Klahr S.** The modification of diet in renal disease study. *N Engl J Med*. 1989;320:864–866.
16. **Kelly TL, Wilson KE, Heymsfield SB.** Dual energy x-ray absorptiometry body composition reference values from NHANES. *PLoS One*. 2009;4:e7038.
17. **Lee EY, Kim D, Kim KM, et al.** Age-related bone mineral density patterns in Koreans (KNHANES IV). *J Clin Endocrinol Metab*. 2012;97:3310–3318.
18. **Myong JP, Kim HR, Choi SE, Koo JW.** Dose-related effect of urinary cotinine levels on bone mineral density among Korean females. *Osteoporos Int*. 2013;24:1339–1346.
19. **Korea Centers for Disease Control and Prevention.** Korea Health Statistics 2009. Korea National Health and Nutrition Examination Survey (KNHANESIV-3). Osong, Korea: Korea Centers for Disease Control and Prevention, Ministry of Health, Welfare; 2010.
20. **Kanis JA, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltaev N.** The diagnosis of osteoporosis. *J Bone Miner Res*. 1994;9:1137–1141.
21. **Beck TJ, Looker AC, Ruff CB, Sievanen H, Wahner HW.** Structural trends in the aging femoral neck and proximal shaft: analysis of the Third National Health and Nutrition Examination Survey dual-energy x-ray absorptiometry data. *J Bone Miner Res*. 2000;15:2297–2304.
22. **Park EJ, Joo IW, Jang MJ, Kim YT, Oh K, Oh HJ.** Prevalence of osteoporosis in the Korean population based on Korea National Health and Nutrition Examination Survey (KNHANES), 2008–2011. *Yonsei Med J*. 2014;55:1049–1057.
23. **Cui LH, Choi JS, Shin MH, et al.** Prevalence of osteoporosis and reference data for lumbar spine and hip bone mineral density in a Korean population. *J Bone Miner Metab*. 2008;26:609–617.
24. **Carballido-Gamio J, Harnish R, Saeed I, et al.** Structural patterns of the proximal femur in relation to age and hip fracture risk in women. *Bone*. 2013;57:290–299.
25. **Vestergaard P.** Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes–a meta-analysis. *Osteoporos Int*. 2007;18:427–444.
26. **Ishii S, Cauley JA, Crandall CJ, et al.** Diabetes and femoral neck strength: findings from the Hip Strength Across the Menopausal Transition Study. *J Clin Endocrinol Metab*. 2012;97:190–197.
27. **Hwang S, Choi HS, Kim KM, Rhee Y, Lim SK.** Associations between serum 25-hydroxyvitamin D and bone mineral density and proximal femur geometry in Koreans: the Korean National Health and Nutrition Examination Survey (KNHANES) 2008–2009. *Osteoporos Int*. 2015;26:163–171.
28. **Bischoff-Ferrari HA, Dietrich T, Orav EJ, et al.** Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. *Am J Clin Nutr*. 2004;80:752–758.
29. **Wicherts IS, van Schoor NM, Boeke AJ, et al.** Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab*. 2007;92:2058–2065.
30. **Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C.** Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *J Bone Miner Res*. 2000;15:1113–1118.
31. **Martin EN, Haney EM, Shannon J, et al.** Femoral volumetric bone density, geometry, and strength in relation to 25-hydroxy vitamin D in older men. *J Bone Miner Res*. 2015;30:475–482.
32. **Jackson RD, Wright NC, Beck TJ, et al.** Calcium plus vitamin D supplementation has limited effects on femoral geometric strength in older postmenopausal women: the Women's Health Initiative. *Calcif Tissue Int*. 2011;88:198–208.
33. **Cauley JA, Lacroix AZ, Wu L, et al.** Serum 25-hydroxyvitamin D concentrations and risk for hip fractures. *Ann Intern Med*. 2008;149:242–250.
34. **Ross AC, Manson JE, Abrams SA, et al.** The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011;96:53–58.
35. **Juul A, Skakkebaek NE.** Androgens and the ageing male. *Hum Reprod Update*. 2002;8:423–433.
36. **Richelson LS, Wahner HW, Melton LJ 3rd, Riggs BL.** Relative contributions of aging and estrogen deficiency to postmenopausal bone loss. *N Engl J Med*. 1984;311:1273–1275.
37. **Riggs BL, Khosla S, Melton LJ 3rd.** Sex steroids and the construction and conservation of the adult skeleton. *Endocr Rev*. 2002;23:279–302.