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 the fracture risk.

Objective: The association of vitamin D with femoral neck (FN) strength.

Designs and Setting: A population-based, cross-sectional study from Korea National Health and Nutrition Examination Surveys.

Participants: 1,209 Koreans (586 men and 623 women) aged $\geq$ 50 years.

Main Outcome Measures: We calculated composite indices of FN strength, such as indices of compression strength (CSI), bending strength (BSI), and impact strength (ISI), 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 CSI, BSI, and ISI 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 = 0.001–0.004). 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 ($\geq$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.

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 highest 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 in order to predict the future fracture risk due to the low sensitivity of BMD for predicting fracture risks (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 forces during a fall (6). These factors suggest that body size and femoral neck (FN) geometry contribute to predicting the fracture risk, independent of the BMD. Karlamanga et al (7) developed the concept of composite indices of FN strength. These indices are composed of FN BMD, FN geometry, and body size in order to determine the structural contributions to bone strength (resistance to fracture forces) relative to load (forces

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Abbreviations:

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 supplement also reduce the 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 the 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 improvement in the 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.

Materials and Methods

Study subjects

This cross-sectional study was based on data acquired in the Fourth Korean National Health and Nutrition Examination Surveys (KNHANES IV), which were 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 website (http://knhanes.cdc.go.kr; available in Korean).

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 as well as information regarding hip geometry and BMD were available for 1632 KNHANES subjects (677 men and 955 women) who were 50 years old or older. Individuals with a history of *any* neoplastic disease, increased serum liver enzyme activity (aspartate aminotransferase (AST) [AST] or alanine aminotransferase (ALT) [ALT] $>$ 100 IU/L), decreased renal function (estimated glomerular filtration rate (GFR) [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 (Ca) and phosphorus (P) intake were collected from all study subjects. Smoking habit was categorized into three levels, ie, never, past or current, and drinking habit was indicated as yes when the subject drank ≥ three units of alcohol per day, respectively. The exercise group was defined as subjects who exercised ≥ 20 minutes per session and ≥ three days/wk, with exercise. Dietary intake of Ca and P were calculated using the 24–hour, dietary recall method. Anthropometric factors such as height (cm) and body weight (kg) were measured using standardized protocols while the subject was dressed in light clothing and without shoes. WC (cm) 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 (DM) was diagnosed using 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 ≥ eight hours, blood samples were drawn from all participants during the survey and were immediately refrigerated and then transported to the Central Testing Institute (Neodin Medical Institute, Seoul, Korea). All blood samples were analyzed within 24 hours following the transportation. Serum 25(OH)D concentrations were measured by competitive radioimmunoassay (RIA) (DiaSorin, Stillwater, MN) using a γ-counter (1,470 Wizard; PerkinElmer, Turku, Finland; reference range 75–250 nmol/L). Serum creatinine concentration was measured colorimetrically using an Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan; reference range 53–106 μmol/L for men and 44–80 μmol/L for women). eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) study formula: eGFR (mL/min/1.73 m2) = [186 $\times$ serum creatinine (mg/dl) $^{-1.154}$] $\times$ age $^{-0.203}$ ($\times$ 0.742 if female) (15).

BMD measurements

In the KNHANES, BMD at the lumbar spine (LS), FN, total femur (TF) was measured using dual-energy X-ray absorptiometry (DXA; QDR 4500A; Hologic Inc, Bedford, MA, USA) 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, and 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, and while getting off and back on 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 standard deviation (SD) at any of sites in the LS, FN, or TF (*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 (NN), as transversing the narrowest FN width. The coefficient of variance (CV) of the HSA indices which were calculated from the same images used for the precision assessment of BMD, was approximately 2%.

Composite indices of FN strength

The indices of compression strength (CSI), bending strength (BSI), and impact strength (ISI) at the FN were measured from the mean FN width (FNW) and hip axis length (HAL), together with the height, weight, and FN BMD for evaluating the FN's capacity 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. The equations for composite indices were previously described by Karlamangla et al (7).

CSI reflects the FN's 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, while 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 (CS-PLAN) which is available as the Complex Samples option in the high SPSS version (SPSS Inc., Chicago, IL, USA). 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 and men was 58.5 (95% CI = 57.3–59.6 years, *range: 50–89 years*) and 56.6 (95% CI = 55.6–57.6, *range: 50–86 years*) years, respectively. Men had a greater height, weight, BMI, eGFR, Ca intake, P 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 analytic methods could rightly analyze the prevalence of osteoporosis in women over 50 years and older but not in those with 50s. The prevalence was similar to those in other studies (22, 23)*. Regular exercise was higher in women than in men, while the percentage of alcohol drinkers and current smokers was lower in women than in men. The mean serum 25(OH) level was 51.8

Table 1. Baseline characteristics of the study population

Characteristic	Women (*n* = 623)	Men (*n* = 586)	*P* value
Age (year)	58.5 (57.3–59.6)	56.6 (55.6–57.6)	0.059
Height (cm)	154.3 (153.7–154.9)	167.5 (166.9–168.0)	<0.001
Weight (kg)	56.6 (55.8–57.5)	67.3 (66.4–68.3)	<0.001
Body mass index (kg/m^2)	23.8 (23.5–24.1)	24.0 (23.7–24.3)	0.203
eGFR (mL/min/1.73m^2)	72.1 (69.1–82.4)	79.0 (76.6–81.3)	<0.001
Alcohol drinker, n (%)	34 (5.5)	256 (43.7)	<0.001
Current smoker, n (%)	44 (7.1)	234 (39.9)	<0.001
Regular exercise, n (%)	109 (17.5)	101 (17.2)	0.609
Calcium intake (mg/day)	412.8 (377.9–447.7)	514.5 (481.5–547.6)	<0.001
Phosphorus intake (mg/day)	951.9 (903.4–1000.4)	1277.5 (1228.4–1326.5)	<0.001
25(OH)D (nmol/liter)	51.8 (49.7–53.9)	61.0 (58.7–63.2)	<0.001
Osteoporosis prevalence, n (%)	249 (39.9)	34 (5.8)	<0.001
Femoral neck BMD (g/cm^2)	0.653 (0.640–0.665)	0.779 (0.767–0.790)	<0.001
Compression SI (g/kg · m)	3.73 (3.66–3.79)	4.25 (4.18–4.32)	<0.001
Bending SI (g/kg · m)	1.19 (1.17–1.21)	1.37 (1.35–1.40)	<0.001
Impact SI (g/kg · m)	0.243 (0.239–0.247)	0.286 (0.281–0.291)	<0.001

Values are presented as the mean with 95% confidence intervals (CIs) unless otherwise specified. *P*-values were determined using the student's *t* test for continuous variables and the χ^2-test for categorical variables. BMD, bone mineral density; eGFR, estimated glomerular filtration rate; SI, strength index; 25(OH)D, 25-hydroxyvitamin D.

(95% CI = 49.7–53.9) nmol/L in women and 61.0 (95% CI = 58.7–63.2) nmol/L in men, respectively.

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 was significantly associated with all composite indices. Also 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 status of diabetes did not generally affect the associations (Supplemental Table 1). This suggests that the noted associations were independent with diabetes. In addition, we divided our subjects into middle aged (50–64 years) and older (≥ 65 years) 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 = .001–0.049). However, some composite indices showed significant or marginal associations with 25(OH)D only in older men, but 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 = 0.001–0.004). 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 0.098, respectively) and those in the Q4 (range: 66.7–136.5 nmol/L) were significantly increased (*P* = .023 and 0.010, 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) which showed the differences in women. The women with high 25(OH)D had consistently higher FN BMD and composite indices

Table 2. Multiple regression analysis performed to determine whether serum 25(OH)D concentrations associate independently with femoral neck BMD and composite indices of femoral neck strength

A) Women

	Independent variables: 25(OH)D (nmol/liter)								
	Unadjusted			**Base model**			**Multivariable model**		
Dependent variables	**β**								
Bending SI (g/kg · m)	**0.001**	**0.001**	**0.249**	**0.001**	**0.001**	**0.071**	**0.002**	**0.001**	**0.047**
Impact SI (g/kg · m)	**0.001**	**0.000**	**0.063**	**0.001**	**0.000**	**0.003**	**0.001**	**0.000**	**<0.001**

B) Men

Dependent variables	Independent variables: 25(OH)D (nmol/liter)								
	Unadjusted			Base model			Multivariable model		
	β	SE.	*P* value[a]	β	SE.	*P* value	β	SE.	*P* value
Femoral neck BMD (g/cm^2)	−0.001	0.001	0.356	0.000	0.001	0.515	0.000	0.001	0.950
Compression SI (g/kg · m)	**0.011**	**0.004**	**0.010**	**0.007**	**0.003**	**0.028**	0.005	0.004	0.076
Bending SI (g/kg · m)	**0.004**	**0.001**	**0.007**	**0.003**	**0.001**	**0.019**	**0.003**	**0.001**	**0.032**
Impact SI (g/kg · m)	**0.001**	**0.000**	**0.002**	**0.001**	**0.000**	**0.008**	**0.001**	**0.000**	**0.027**

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

Base model: adjustment for age, height, weight, and waist circumference.

Multivariable model: adjustment for age, height, weight, waist circumference, estimated glomerular filtration rate, alcohol status (≥3 U/day), smoking status, exercise status (≥30 min/day), calcium intake, and phosphorus intake.

Bold font indicates that the differences were statistically significant.

BMD, bone mineral density; SE., standard error; SI, strength index; 25(OH)D, 25-hydroxyvitamin D

Table 3. Multiple regression analysis performed to determine whether serum 25(OH)D concentrations associate independently with femoral neck BMD and composite indices of femoral neck strength according to their age

A) Women

	Independent variables: 25(OH)D (nmol/liter)											
	Age 50–64 yr old (*n* = 394)							**Age ≥65 yr old (*n* = 229)**				
Dependent variables	**Unadjusted**											
Femoral neck BMD (g/cm²)	**0.001**	**0.001**	**0.292**	**0.001**	**0.000**	**0.067**	**0.002**	**0.001**	**0.004**	**0.002**	**0.001**	**0.001**
Compression SI (g/kg · m)	0.005	0.003	0.070	**0.007**	**0.002**	**0.004**	**0.011**	**0.005**	**0.020**	**0.013**	**0.003**	**0.002**
Bending SI (g/kg · m)	0.001	0.001	0.512	**0.002**	**0.001**	**0.027**	0.003	0.002	0.139	**0.003**	**0.002**	**0.049**
Impact SI (g/kg · m)	0.000	0.000	0.240	**0.001**	**0.000**	**0.009**	**0.001**	**0.000**	**0.018**	**0.001**	**0.000**	**0.001**

B) Men

Dependent variables	Independent variables: 25(OH)D (nmol/liter)											
	Age 50–64 yr old (*n* = 396)						Age ≥65 yr old (*n* = 190)					
	Unadjusted			Multivariable model			Unadjusted			Multivariable model		
	β	SE.	*P* value[a]	β	SE.	*P* value	β	SE.	*P* value[a]	β	SE.	*P* value
Femoral neck BMD (g/cm²)	0.001	0.001	0.510	0.000	0.001	0.683	0.000	0.001	0.749	0.002	0.001	0.205
Compression SI (g/kg · m)	0.006	0.005	0.225	0.005	0.003	0.194	**0.031**	**0.007**	<**0.001**	0.012	0.008	0.123
Bending SI (g/kg · m)	0.003	0.002	0.108	0.002	0.001	0.071	**0.009**	**0.003**	**0.001**	0.004	0.003	0.130
Impact SI (g/kg · m)	0.001	0.000	0.130	0.000	0.000	0.106	**0.002**	**0.001**	<**0.001**	**0.001**	**0.000**	**0.049**

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

Base model: adjustment for age, height, weight, and waist circumference.

Multivariable model: adjustment for age, height, weight, waist circumference, estimated glomerular filtration rate, alcohol status (≥3 U/day), smoking status, exercise status (≥30 min/day), calcium intake, and phosphorus intake.

Bold font indicates that the differences were statistically significant.

BMD, bone mineral density; SE., standard error; SI, strength index; 25(OH)D, 25-hydroxyvitamin D

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 difference 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.

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 [illegible]tion, compared to BMD alone (7). For ex- [illegible] having a high BMD, diabetic patients usu- [illegible] incidence of FN fracture compared to the [illegible]ation (25). The increased fracture risk in [illegible] diabetes is consistent with the lower com- [illegible]een in persons with diabetes relative to non-

[illegible]ct of 25(OH)D levels on FN BMD, recent [illegible]NHANES data similar to our study popu- [illegible] that high 25(OH)D levels were associated

A women

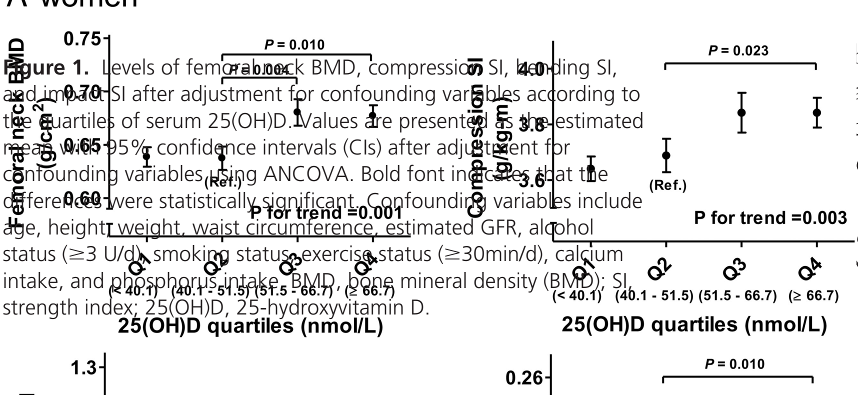

Figure 1. Levels of femoral neck BMD, compression SI, bending SI, and impact SI after adjustment for confounding variables according to the quartiles of serum 25(OH)D. Values are presented as the estimated mean with 95% confidence intervals (CIs) after adjustment for confounding variables using ANCOVA. Bold font indicates that the differences were statistically significant. Confounding variables include age, height, weight, waist circumference, estimated GFR, alcohol status (≥3 U/d), smoking status, exercise status (≥30min/d), calcium intake, and phosphorus intake. BMD, bone mineral density (BMD); SI, strength index; 25(OH)D, 25-hydroxyvitamin D.

Table 4. Femoral neck BMD and composite indices of femoral neck strength relative to serum 25(OH)D levels in women

	Unadjusted			Base model			Multivariable model		
	25(OH)D <51.5 nmol/liter	25(OH)D ≥51.5 nmol/liter		25(OH)D <51.5 nmol/liter	25(OH)D ≥51.5 nmol/liter		25(OH)D <51.5 nmol/liter	25(OH)D ≥51.5 nmol/liter	
	Estimated mean (95% CI)		*P* value	Estimated mean (95% CI)		*P* value	Estimated mean (95% CI)		*P* value
Femoral neck BMD(g/cm^2)	**0.642 (0.626–0.658)**	**0.674 (0.653–0.694)**	**0.016**	**0.639 (0.627–0.652)**	**0.677 (0.663–0.691)**	**<0.001**	**0.638 (0.626–0.650)**	**0.679 (0.665–0.693)**	**<0.001**
Compression SI (g/kg · m)	3.69 (3.60–3.77)	3.81 (3.71–3.91)	0.068	**3.66 (3.60–3.73)**	**3.84 (3.76–3.91)**	**0.001**	**3.66 (3.60–3.73)**	**3.84 (3.77–3.92)**	**0.001**
Bending SI (g/kg · m)	1.19 (1.16–1.21)	1.21 (1.18–1.25)	0.214	**1.18 (1.16–1.21)**	**1.22 (1.19–1.25)**	**0.047**	**1.18 (1.16–1.20)**	**1.22 (1.19–1.25)**	**0.025**
Impact SI (g/kg · m)	**0.240 (0.234–0.245)**	**0.248 (0.242–0.255)**	**0.046**	**0.238 (0.234–0.243)**	**0.250 (0.245–0.255)**	**0.001**	**0.238 (0.234–0.243)**	**0.250 (0.245–0.255)**	**0.001**

Estimated means with 95% confidence intervals (CIs) before and after adjustment for confounding variables, were generated and compared using analysis of covariance (ANCOVA).

Base model: adjustment for age, height, and weight, and waist circumference.

Multivariable model: adjustment for age, height, weight, waist circumference, estimated glomerular filtration rate, alcohol status (≥3 U/day), smoking status, exercise status (≥30 min/day), calcium intake, and phosphorus intake.

Bold font indicates that the differences were statistically significant.

BMD, bone mineral density; SI, strength index; 25(OH)D, 25-hydroxyvitamin D.

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, our study showed the trend to higher FNW as a parameter of hip geometry in men with high 25(OH)D levels despite marginally statistical significance in only men. 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 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 the 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 more than 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 seven years (adjusted odds ratio (AOR) = 1.71, 95% CI = 1.05–2.79) (33). Recently the Institute of Medicine of the U.S. 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 the fracture risk.

In our study, the associations of higher 25(OH)D levels with higher bone strength were more dominant in women, compared to men. The reason for these differences by gender is 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 (50–64 years) additionally implicate this possibility because sex hormone alterations is less significant in the 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 result 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 testosterone, may have an influence on hip geometry. Therefore, our current results indicate that middle aged adults, especially women undergoing this dynamic period of menopause which 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 sex hormone's role 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, and which enhances the statistical reliability of the results and the generalizability of the data. Our study also has several limitations. First, as it was cross-sectional in design, the observed associations between 25(OH)D and the composite indices of may not indicate a cause-and-effect relationship. Second, as serum concentrations of calcium, phosphate and parathyroid hormone 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 as 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 (CT), 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.

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