ORIGINAL ARTICLE

Unraveling the relationship between serum 25-hydroxyvitamin D levels and trabecular bone score in American adults

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KEY WORDS

ABSTRACT

INTRODUCTION Trabecular bone score (TBS) is a novel way for clinicians to evaluate bone quality. It is directly associated with the mechanical strength of bones and helps predict fractures. Vitamin D, a secosteroid that enhances calcium absorption, is commonly used to strengthen the skeletal system.

OBJECTIVES The present analysis aimed to determine the relationship between vitamin D levels and TBS by analyzing data from the National Health and Nutrition Examination Survey.

PATIENTS AND METHODS A total of 4464 persons (2148 men and 2316 women) were included in our study. The participants were analyzed according to sex, obesity status, and T-score using regression models.

RESULTS We noted a remarkably positive relationship between serum levels of 25-hydroxyvitamin D (25[OH]D) and TBS after the results were fully adjusted ($\beta = 0.319$; 95% CI, 0.145–0.494; $P < 0.001$). T-score analysis showed that serum 25(OH)D levels were related to TBS in the group of participants with normal bone mineral density (T-score > -1) ($\beta = 0.311$; 95% CI, 0.097–0.525; $P = 0.005$). However, in the osteopenia (T-score between -1 and -2.5) and osteoporosis (T-score < -2.5) group there was no such association ($P > 0.05$).

CONCLUSIONS Our study shows that low serum levels of 25(OH)D may decrease the TBS, which represents the skeletal microarchitecture and is a fracture risk factor in individuals with normal T-scores.

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INTRODUCTION Osteoporosis is a systemic skeletal disorder that leads to bone fragility and an increased risk of low-energy fractures. In the 21st century, approximately 36% to 53% of women and 19% to 36% of men over the age of 50 years have osteopenia at the femur neck or lumbar spine, whereas 10% to 17% of women and 3% to 5% of men have osteoporosis at these sites.[1] Annually, more than 2 million Americans experience low-trauma fractures, which generates a cost of nearly USD 13.7–20.3 billion.[2] Furthermore, previous studies demonstrated that a high risk of osteoporotic fractures constitutes a significant disease burden to the society, and it may increase markedly in the future.[3]

To date, the gold standard in the diagnosis of osteoporosis is the measurement of bone mineral density (BMD) through central dual-energy X-ray absorptiometry (DXA).[4] However, BMD only provides information on bone quantity, with no data regarding bone quality. A considerable overlap in BMD values exists between individuals who develop fractures and those who do not.[5] This indicates that BMD sensitivity to predict fractures is low. For example, based on BMD, patients with type 2 diabetes have a higher risk of fracture than nondiabetic individuals.[6] Thus, factors other than bone mass influence the bone strength and fracture risk.

In addition to DXA, radiofrequency echographic multispectrometry (REMS) is another tool that

WHAT'S NEW?

Osteoporosis is a major clinical problem in older people. It affects the structure and strength of bones. Vitamin D is an important nutrient related to bone quantity. In our analysis of data from the National Health and Nutrition Examination Survey, we found a positive association between serum vitamin D levels and the trabecular bone score, regardless of sex or the presence of obesity. We also showed that serum vitamin D levels were strongly related to bone health, in terms of both quantity and quality. Our study indicates that early interventions, including lifestyle changes or nutritional support, may help prevent osteoporosis.

may be used in the diagnosis of osteoporosis. By means of radiofrequency ultrasound signals, REMS estimates the bone strength and predicts fracture risk.[7] However, operator-dependent errors were observed, for example, selecting an incorrect depth or focus at echographic scanning. In comparison with DXA, a more rigorous operator training is needed in REMS to ensure its full clinical practicability.[8]

Trabecular bone score (TBS) is a novel way to clinically evaluate bone quality. Derived from the lumbar spine DXA imaging, TBS reflects the bone microarchitecture based on a novel gray-level texture measurement.[9] It is directly related to the mechanical strength of the bone and helps predict fractures.[10] Recent studies showed that the Fracture Risk Assessment Tool (FRAX) score in combination with TBS can predict fracture risk more accurately than FRAX alone.[11]

Vitamin D, a secosteroid that enhances the absorption of calcium, magnesium, and phosphate, is commonly used to strengthen the bones.[12] Vitamin D_3 (cholecalciferol) is more common in clinical practice.[13] The main way of synthesizing cholecalciferol is through sun exposure. Subclinical vitamin D deficiency (<30 ng/ml) is related to osteoporosis and a higher incidence of falls or fractures.[14] Severe vitamin D deficiency (<5 ng/ml) may cause rickets in infants or children and osteomalacia in adults.

Previous reports investigated the associations of clinical factors and TBS with high doses of supplemental vitamin D.[15] However, no study has yet analyzed the relationship between serum 25-hydroxyvitamin D (25[OH]D) levels and TBS in the general population. This analysis aimed to determine such a relationship by examining data from the National Health and Nutrition Examination Survey (NHANES).

PATIENTS AND METHODS **Study design and participants** We obtained all data from the 2005–2006 NHANES database administered by the National Center for Health Statistics (NCHS), including demographic information, laboratory data, and medical history. We included 4464 individual (2148 men and 2316 women). After excluding patients with incomplete data, our study cohort comprised 2332 individuals with normal BMD (T-score >–1), 688 individuals with osteopenia (T-score between

–2.5 and –1), and 112 persons with osteoporosis (T-score <–2.5).

Bone parameters Whole body DXA exams in the NHANES were performed according to the procedures recommended by the manufacturer on a QDR 4500A fan beam densitometer (Hologic, Inc., Bedford, Massachusetts, United States). The results were reviewed and analyzed by the Bone Density Group at the Department of Radiology, University of California, San Francisco using industry-standard techniques. Analysis of all examinations was performed using Hologic Discovery software, version 12.1 (Hologic, Inc., Marlborough, Massachusetts, United States) in default configuration. BMD and TBS were measured by DXA at the lumbar spine (L1–L4). TBS was measured with TBS iNsight software (Medimaps Group SA, Plan-les-Ouates, Switzerland). The results were derived from a patented algorithm that evaluated pixel gray levels and spatial variations in raw anteroposterior spine images. The TBSs of the L1–L4 vertebrae were averaged.

25-hydroxyvitamin D level measurement The serum concentration of 25(OH)D was measured by an enzyme immunoassay. Based on the previous studies[14,16], the serum 25(OH)D level was categorized into 2 groups: deficient (<75 nmol/l) and sufficient (≥75 nmol/l).

Covariate assessments Demographic data were self-reported by the participants during the initial screening questionnaire. Body mass index (BMI) was calculated as body mass in kilograms divided by the height in meters squared. Other medical history data, such as a history of fracture, congestive heart failure, angina or angina pectoris, and stroke were identified through positive answers to questions regarding these conditions. Smoking status was assessed with the item, "Smoked at least 100 cigarettes over lifetime."

Statistical analysis All analyses were performed using SPSS, version 18 (SPSS, Inc., Chicago, Illinois, United States). Descriptive data are presented as median (interquartile range) and number (percentage) of observations, for continuous and categorical variables, respectively. The comparison of characteristics and covariates across subgroups was performed by the *t* test for continuous variables and the χ^2 test for categorical variables. We analyzed the association between serum 25(OH)D levels and TBS using a univariable linear regression model. The β coefficient represented the degree of change in the TBS for every 1-unit change in the serum 25(OH)D level. A 2-sided *P* value below 0.05 was considered significant. TBS was the dependent variable, and the serum 25(OH)D level was the independent variable. Three models were executed to adjust for covariates: Model 1 was adjusted for age, sex, ethnicity, BMI, and total spine

TABLE 1 Characteristics of the study participants according to vitamin D levels

Characteristics		25(OH)D level		P value
		Deficient: <75 nmol/l (n = 3635)	Sufficient: ≥75 nmol/l (n = 829)	
Age, y		47 (33–64)	42 (29–62)	0.02
Male sex		1797 (49)	351 (42)	<0.001
Ethnicity	Mexican American	825 (22)	83 (10)	<0.001
	Other Hispanic	116 (3)	21 (2)	
	Non-Hispanic White	1585 (43)	663 (79)	
	Non-Hispanic Black	985 (27)	40 (4)	
BMI, kg/m^2		28.19 (24.63–32.68)	25.86 (23.21–29.34)	<0.001
TBS		1.38 (1.27–1.47)	1.42 (1.33–1.50)	<0.001
Total spine BMD, gm/cm^2		1.03 (0.94–1.14)	1.03 (0.94–1.12)	0.01
Fasting glucose, mg/dl		99 (91–108)	95 (87–103)	<0.001
CRP, mg/dl		0.24 (0.09–0.57)	0.19 (0.08–0.44)	0.01
HDL-C, mg/dl		51 (42–62)	58 (46–70)	0.04
Creatinine, mg/dl		0.9 (0.8–1.1)	0.9 (0.7–1.0)	0.05
AST, U/l		23 (20–28)	23 (20–28)	0.51
Total calcium, mg/dl		9.5 (9.2–9.7)	9.5 (9.2–9.7)	0.37
Phosphorus, mg/dl		3.8 (3.4–4.2)	3.8 (3.5–4.2)	0.83
Smoking		1678 (46)	436 (52)	0.001
Alcohol consumption		2244 (61)	607 (73)	<0.001
Fracture history	Hip	54 (1)	9 (1)	0.48
	Wrist	335 (9)	99 (11)	0.03
	Spine	87 (2)	26 (3)	0.37
Congestive heart failure		131 (3)	17 (2)	0.07
Coronary heart disease		153 (4)	22 (2)	0.10
Cancer		281 (7)	89 (10)	0.01

Data are presented as median (interquartile range) or number (percentage) of patients.

SI conversion factors: to convert glucose to mmol/l, multiply by 0.055; CRP to mg/l, by 10; HDL-C to mmol/l, by 0.026; creatinine to µmol/l, by 88.4; AST to µkat/l, by 0.0166; calcium to mmol/l, by 0.25; phosphorus to mmol/l, by 0.323.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AST, aspartate aminotransferase; BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; TBS, trabecular bone score

BMD. Model 2 included all variables from Model 1 and was further adjusted for fasting glucose, C-reactive protein (CRP), high-density lipoprotein cholesterol (HDL-C), creatinine, aspartate aminotransferase (AST) as well as total calcium and phosphorus levels. Model 3 included all variables from Model 2 and was further adjusted for fracture history, congestive heart failure, coronary heart disease, cancer, smoking status, and alcohol consumption.

Ethical considerations The data collection protocols were created by NCHS of the Centers for Disease Control and Prevention and approved by the NCHS Institutional Review Board.

RESULTS **Participant characteristics** Demographic characteristics of the participants stratified by the serum 25(OH)D level are presented in TABLE 1. The median (IQR) age of the group with a sufficient level of 25(OH)D was 42 (29–62) years, and the median age of the group deficient in 25(OH)D was 47 (33–64) years. The group with a sufficient 25(OH)D level had a lower BMI as well as fasting glucose and CRP levels, and higher TBS, BMD, and HDL-C and total calcium levels (P <0.05).

Association between serum 25-hydroxyvitamin D levels and trabecular bone score The relationship between the serum 25(OH)D level and TBS is presented in TABLE 2. In an ungrouped analysis, we found a significant association between serum 25(OH)D level and TBS. After adjusting for all covariates, the β coefficient of the serum 25(OH)D level was 0.319 (95% CI, 0.145–0.494; P <0.001).

Sex differences in the relationship between serum 25-hydroxyvitamin D levels and trabecular bone score A linear regression of the sex-specific association between the serum 25(OH)D level and TBS is shown in TABLE 3. A significant association was found in both men (β = 0.640; 95% CI, 0.243–1.037; P =0.002) and women (β = 1.226; 95% CI, 0.848–1.603; P <0.001). After adjusting for all covariates, positive associations were still noted in both sexes (β = 0.468;

TABLE 2 Association between the serum vitamin D level and the trabecular bone score

Variable	Unadjusted model	P value	Model 1	P value	Model 2	P value	Model 3	P value
25(OH)D level, nmol/ml	0.939 (0.665–1.213)	<0.001	0.318 (0.144–0.492)	<0.001	0.278 (0.104–0.452)	0.002	0.319 (0.145–0.494)	<0.001

Data are presented as β coefficient (95% CI).

Adjusted covariates: Model 1 = age, sex, race, BMI, total spine BMD; Model 2 = Model 1+ fasting glucose, CRP, HDL-C, creatinine, AST, total calcium, total phosphorus; Model 3 = Model 2 + fracture history, congestive heart failure, coronary heart disease cancer + smoking, alcohol consumption

Abbreviations: see TABLE 1

TABLE 3 Sex- and body mass index–specific association between the serum vitamin D level and the trabecular bone score

25(OH)D level, nmol/ml	Men		Women	
	β (95% CI)	P value	β (95% CI)	P value
Unadjusted model	0.640 (0.243–1.037)	0.002	1.226 (0.848–1.603)	<0.001
Model 1	0.428 (0.186–0.670)	0.001	0.316 (0.077–0.556)	0.01
Model 2	0.376 (0.131–0.621)	0.003	0.309 (0.072–0.546)	0.01
Model 3	0.468 (0.224–0.712)	<0.001	0.315 (0.075–0.554)	0.01
25(OH)D level, nmol/ml	BMI <30 kg/m²		BMI ≥30 kg/m²	
Unadjusted model	0.306 (0.065–0.547)	0.01	0.856 (0.265–1.447)	0.005
Model 1	0.264 (0.106–0.421)	0.001	0.696 (0.291–1.101)	0.001
Model 2	0.229 (0.070–0.388)	0.005	0.702 (0.301–1.103)	0.001
Model 3	0.255 (0.095–0.415)	0.002	0.748 (0.345–1.150)	<0.001

Adjusted covariates: see TABLE 2

Abbreviations: see TABLE 1

95% CI, 0.224–0.712; P <0.001 and β = 0.315; 95% CI, 0.075–0.554; P = 0.01, respectively, for men and women).

Body mass index and the relationship between serum 25-hydroxyvitamin D levels and trabecular bone score The association between the serum 25(OH)D level and TBS in patients stratified by BMI is presented in TABLE 3. Obesity status analysis showed that the association between serum 25(OH)D level and TBS was significant in both the obese and nonobese groups. After full adjustments, the β coefficients of the serum 25(OH)D levels were 0.748 (95% CI, 0.345–1.150; P <0.001) in the obese group and 0.255 (95% CI, 0.095–0.415; P =0.002) in the nonobese group.

T-score and the relationship between serum 25-hydroxyvitamin D levels and trabecular bone score The impact of the T-score on the relationship between serum 25(OH)D levels and TBS is shown in TABLE 4. T-score analysis showed that the association between serum 25(OH)D level and TBS remained positive in the normal BMD group (T-score > –1) in all models. The β coefficient of the serum 25(OH)D level was 0.311 (95% CI, 0.096–0.525; P = 0.005) in this group after all adjustments. However, there was no significant association between the serum 25(OH)D level and TBS in the osteopenia (T-score between –1 and –2.5) and osteoporosis (T-score <–2.5) groups.

DISCUSSION In this cross-sectional study of American adults, we analyzed the independent effects of serum 25(OH)D levels on TBS in 4464 individuals and revealed an independent association between these 2 variables. We demonstrated a positive association between the serum 25(OH)D level and TBS in both men and women after adjustment for all covariates. Furthermore, the association was positive regardless of the obesity status. In subgroups divided according to T-scores, the significant association between serum 25(OH)D level and TBS was evident only in the participants with normal BMD (T-score >–1). Based on these results, it can be inferred that early interventions, including lifestyle changes or nutritional support, may help prevent osteoporosis.

Previous studies used quantitative computed tomography (QCT) and peripheral QCT to investigate the relationship between bone microarchitecture and serum 25(OH)D levels.[17-19] They revealed a weak association between these 2 factors. A recently developed analytical tool, TBS, has rarely been used in the assessment of the impact of serum 25(OH)D levels on bone microarchitecture. In studies involving adults, the preservation of bone mass and microarchitecture of the spine has been reported with combined calcium and vitamin D supplementation[20]; however, correction of vitamin D insufficiency (≥30 ng/ml) in postmenopausal women showed no clinically meaningful beneficial effects on BMD.[16]

TABLE 4 Association between the serum vitamin D level and the trabecular bone score according to T-scores

25(OH)D level, nmol/ml	Total spine BMD T-score <–2.5		Total spine BMD T-score –2.5 to –1		Total spine BMD T-score >–1	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Unadjusted model	0.942 (–0.403 to 2.287)	0.16	0.813 (0.208–1.419)	0.009	0.965 (0.664–1.266)	<0.001
Model 1	0.363 (–0.885 to 1.610)	0.56	0.229 (–0.185 to 0.643)	0.27	0.311 (0.096–0.525)	0.005
Model 2	0.649 (–0.856 to 2.155)	0.38	0.150 (–0.274 to 0.574)	0.48	0.282 (0.068–0.496)	0.01
Model 3	1.009 (–0.603 to 2.622)	0.21	0.221 (–0.212 to 0.653)	0.31	0.311 (0.097–0.525)	0.005

Adjusted covariates: see TABLE 2

Abbreviations: see TABLE 1

Walker et al[21] reported that TBS did not differ in patients with primary hyperparathyroidism stratified by the vitamin D level (range, 14–65 pg/ml). It was suggested that the maternal 25(OH)D level correlated with TBS in the offspring's vertebral microarchitecture.[22] Another study showed that vitamin D treatment in vitamin D-deficient pediatric populations could result in clinically significant improvements in measures of bone mass.[23] However, the relationship between 25(OH)D and TBS is less frequently mentioned. A study by Donaldson et al[24] showed no association between 25(OH)D and TBS in patients with anorexia, while a study of healthy, school-age children reported no benefit of vitamin D supplementation.[25] Here, we demonstrated a strong relationship between serum 25(OH)D levels and TBS in American adults.

Bone formation and strength rely on sufficient calcium supply from intestinal and renal reabsorption. Vitamin D- and $1,25(OH)_2D_3$-regulated calcium transport occurs in the duodenum, ileum, cecum, and colon by the apical membrane calcium channel.[26] The regulation of calcium reabsorption in the distal tubules is associated with $1,25(OH)_2D_3$ and parathyroid hormone (PTH) levels.[27] Furthermore, vitamin D participates in bone homeostasis by stimulating osteoblasts and osteoclasts. Previous studies discussed the relationship between vitamin D and bone parameters. Winzenberg et al[23] suggested that vitamin D supplementation in vitamin D-deficient populations could result in improved bone mass. However, vitamin D supplementation in children and adolescents with normal vitamin D levels provided no benefit. Another study showed that low concentrations of vitamin D accompanied by high bone mass resorption limited the accretion of bone mass in young girls.[28] The relationship between 25(OH)D levels and TBS is less clear. Our results showed a strong, significant association between serum 25(OH)D levels and TBS, regardless of sex or the presence of obesity.

Interestingly, in the T-score–specific analysis, the positive association between serum 25(OH)D levels and TBS was only evident in the individuals with normal BMD (T-score >–1). This may have been caused by the small number of participants with osteopenia and osteoporosis in our study. However, we propose 2 other hypotheses explaining these results. First, the patients with osteoporosis had multiple impaired mechanisms of bone homeostasis. For example, estrogen deficiency, cytokines including tumor necrosis factor α and interleukin 6, and intracellular reactive oxygen species may cause osteoporosis. In their review, Bolland et al[29] discussed whether calcium or vitamin D supplements could be used to treat osteoporosis. A meta-analysis of 26 randomized controlled trials of calcium supplementation with and without vitamin D showed no additional effects on the fracture risk. Other 23 randomized controlled trials indicated that vitamin D supplementation with or without calcium did not affect the total risk for fractures. On the other hand, a study of patients with Crohn disease showed that lower T-scores and Z-scores were observed in the individuals with Crohn disease taking vitamin D supplements than in those who did not.[30] The evidence suggested that in addition to vitamin D deficiency, there were still many different mechanisms potentially leading to osteoporosis.

Second, the vitamin D receptor might be desensitized in patients with osteoporosis. A 2014 cohort study examined the association between 4 single-nucleotide polymorphisms (rs7975232, rs1544410, rs2239185, and rs3782905) of the vitamin D receptor gene and osteoporosis.[31] It demonstrated that genetic polymorphisms were associated with osteoporosis in elderly people.

The strength of the present study is the large population of included participants. Moreover, we examined many confounders and discussed their connections with the exposure and outcome. However, there are also several limitations that need to be mentioned. First, due to the fact that they were retrieved from a cross-sectional database, the serum 25(OH)D level and TBS were determined in a single measurement and their assessment was not repeated over time. In addition, the 2005–2006 NHANES database lacked the time of the year the vitamin D level was assessed. Second, osteoporosis is the most prevalent in the aging population, whereas our study cohort was relatively young. The small number of individuals with osteoporosis and osteopenia increased the risk of a false negative or type II error. Third, we assessed TBS by DXA, and the operators' technique might have affected the measurement. Finally, we did not present PTH levels in our study. Increased PTH levels might reduce TBS values, which could have affected the results.

Further studies evaluating the impact of vitamin D on TBS are needed to verify our research results.

Conclusions Our study identified the impact of serum 25(OH)D levels on TBS in a population of American adults. Previous analyses provided evidence regarding the relationship between TBS and fracture risk. Our results show that low vitamin D levels may decrease TBS, which represents the skeletal microarchitecture, and increase the risk of fracture in individuals with a normal T-score.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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