The Effects of Vitamin Dand Sarcopenia on Bone Mineral Densityin Korean women

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ABSTRACT

A osteoporotic fracturehasbecome a global health issue that causes tremendous impact on mortality as well as heavy socioeconomic burden. Previous studies suggestedthat vitamin D may prevent fractures by improving muscle mass as well as via increasing bone density directly.The purpose of the study is to determine thatthe influence of vitamin D on bone mineral density depends on its effects on muscle mass.

We analyzed the data from Korean National Health and Nutritional Survey IV in 2009.Women older than age 20 were included for the analyses.Bone mineral density and muscle mass were measured by DXA. Serum vitamin D concentration was tested.

Vitamin D and muscle mass affected BMD at proximal femur, but not at lumbar spine. Vitamin D deficiency and sarcopenia increased odd ratio for osteoporosis before and after adjusted for multiple variables. The effects of vitamin D deficiency on BMD still remained significant after adjustment for sarcopenia, which was vice versa.

Though vitamin D deficiency and sarcopenia shared common effects on BMD, they have their own effects on BMD independent from each other.

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CHAPTER 1. INTRODUCTION

1.1 Background

A osteoporotic fracturehasbecome a global health issuethat cause tremendous impact on mortality as well as heavy socioeconomic burden.The estimated number of new osteoporotic fractures for the year 2000 was 9.0 million and fracture sufferers were estimated at 56 million worldwide, [1] Osteoporotic hip fractures cause the most morbidity with reported mortality rates up to 20-24% in the first year after a fracture, and greater risk of death persists for at least 5 years afterwards. Osteoporosis in Europe also contributed to a higher burden than the common neoplastic disorders, save only for lung cancer.[2] In 2004, the estimated cost of treating patients hospitalized with a diagnosis of osteoporosis was $19.1 billion

Vitamin D is anessential hormone for absorption of calcium in intestine and mineralization ofbone. Lips P et al. (2001) showed that inadequate serum vitamin D concentration leads to insufficient mineralization of bone and results inosteomalacia and osteoporosis. [3] The National Health and Nutrition Examination Survey (NHANES)showed that bone mineral density (BMD) correlates positively with 25-hydroxy vitamin D (25(OH) D) concentration in Caucasian women. [4]Vitamin D also reportedly has positive effects on skeletal muscle and strength. Several studies insinuated that vitamin D may influence BMD via its beneficial effects on skeletal muscle. [8,9]Several studies have shown a positive relationship between lean mass and BMD.[5, 6] Women with osteoporosisshowed significantly lower appendicular skeletal muscle mass,relative toage-matched controls without osteoporosis.[7]

1.2 Objectives

The purpose of the study is to determine that the positive influence of vitamin D on BMD depends on its beneficial effects on muscle mass.

CHAPTER 2. METHODOLOGY

2.1 Study Participants

This study is based upon the data acquired during the second year (2009) of KNHANES IV, cross-sectional and nationally representative survey conducted by the Division of Chronic Disease Surveillance, Korea Centers for Disease Control and Prevention. Data were collected via household interviewsand direct standardized physical examinations conducted in specially equipped mobile examination centers.

The sampling frame was developed based on the 2005 population and housing census in Korea. Household units were selected by a stratified multistage probability sampling design. Two hundred national districts from primary sampling units were randomly sampled, in 2009. Finally, 10078 participated in the health interviews and health examination surveys. We combined the data collected from 7920 participants of KNHANES (ALL) and 8320 participants of KHNANES (DXA) in this study. Among them 3820 women older than 20 years were selected. Premenopausal women who are free from osteoporosis treatment, renal failure and any type of cancer were determined as reference population.

2.2 Definition of osteoporosis, sarcopenia and vitamin D deficiency

DXA (Hologic Discovery-W; Hologic) was used for the measurement of bone mineral density and appendicular muscle mass of the participants.

We use WHO definition, BMD value of 2.5 standard deviation or more below mean for normal young adult or t score of -2.5 to be defined as osteoporosis. Those less than but not reaching -2.5 standard deviation is regarded as osteopenia.

Appendicular Skeletal Mass (ASM) was calculated as the sum of muscle mass in arms and legs, assuming that all nonfat and non-bone tissue is skeletal muscle. Weight-adjusted ASM (total ASM divided by weight x 100) and height adjusted ASM (total ASM divided by height squared) [10]. The calculated weight adjusted ASM value between mean value (28.05%) and 2 standard deviation (24.23%) of reference population is regarded as type 1 sarcopenia and below the 2 standard deviation value is regarded as type 2 sarcopenia (Jansen et. al and Lim et. al).

Serum 25(OH)D levels were measured using a gamma counter (1470 Wizard, Perkin-Elmer) with an radio immunoassay (DiaSorin, Still- water, MN25-hydroxyvitamin D (25(OH) D) level between 10-20 ng per milliliter (25nmol per liter) is considered insufficient and below 10ng/dl is considered deficient in Korean population. (Y.-C Hwang et al: Optimal 25-hydroxyvitamin D level for bone (2012)) [11]

2.3 Statistical analysis

Statistical analyses were performed using SPSS software for Mac version 19.0 (SPSS Inc., Chicago, IL). The mean value and standard deviations of gender specific baseline characteristics (age, weight, height, BMI), and body composition including bone mineral density (total, femur, hip, lumbar) were done.Groups of BMDs, vitamin D and weight-adjusted muscle were formed according to cut-off values. The mean and standard deviation values were grouped into 2 and compared according to sarcopenia status by independent T test. The bivariate correlation and partial correlation after adjusting age and BMI, menstrual status moderate exercise and calcium intakeamong the bone mineral densities, vitamin D, and weight adjusted muscle mass were tested. The odd ratios of sarcopenia and vitamin D deficiency on bone mineral density(BMD) and Vitamin D deficiency on BMD, unadjusted and adjusted for multiple levels were analyzed bylogistic regression tests.

CHAPTER 3. PRESENTATION OF RESULTS

3.1 General characteristics of study populataion

3820 women from age 20 to 91 were included for the analyses. Sarcopenic women were older, shorter in height, and more overweighted than non sarcopenic women. Sarcopenic group had less muscle mass and more fat massthan non-sarcopenic groupbefore and after adjusted for weight or height. Vitamin D concentration and BMD were lower in sarcopenic women, compared to the non-sarcopenic. Daily protein intake was less in sarcopenic group than in non-sarcopenic group while calcium intake did not differ between groups.

Table 1. Demographic characteristicsof study subjects

(Mean ± SD)

	Non- sarcopenic Women (n=3642)	**Sarcopenicwomen (n=178)**
Age	48.7 ±16.0	60.5±14.5**
Height (cm)	156.6 ±6.5	150.8±5.9**
Weight (kg)	56.4 ±87.5	62.8±10.8**
BMI (kg/m^2)	23.0 ±3.2	27.6±4.1**
total fat (g)	18291.18±5028.62	26546.77±5951.63**
Total fat percentage (%)	32.0 ±4.9	42.0±3.5**
ASM (g)	15911.34 ±2496.60	15293.83 ±2218.34**
Weight adjusted ASM (%)	27.8±2.4	21.9±1.4**
Height adjusted ASM (Kg/m^2)	0.6087±0.1046	0.4738±0.2746**
Vitamin D (ng/ml)	17.2 ±6.3	16.0 ±6.2*
Whole body BMD (g/cm^2)	1.091±0.136	1.046±1.350**
Lumar spine L1-4 BMD (g/cm^2)	0.903±0.160	0.874±0.152*
Femoral neck BMD (g/cm^2)	0.701±0.129	0.651±0.138**
Total femur BMD (g/cm^2)	0.853±0.132	0 .813±0.139**
Daily protein intake (g)	55.8±27.9	45.8±22.5**
Daily calcium intake (g)	436.69±246.09	380.23±249.133
Moderate exercise (%)	14.3	12.9

** : P value <0.01

*: P value <0.05

BMI :Body massindex

BMD : Bone mineral density

ASM : Appendicular skeletal muscle mass

3.2 Correlation amongserum Vitamin D, appendicular skeletal muscle mass and BMD.

In bivariatecorrelation, vitamin D positively correlated only with height adjusted ASM , not with weight adjusted ASM before and after adjusted for age, mentrual status, daily calcium intake and moderate exercise.Though vitamin D concentration did not show a correlation with femoral BMDs and even negative correlation with lumbar BMD in unadjusted model, after the adjustment, vitamin D had weak but significant correlations with femoral neck and total femur BMD while negative correlation betweeen vitamin D and lumbar BMD disappeared. Weight adjusted and height adjusted ASM had significant positive correlations with all BMDs. Strength of correlation between any BMDs and height adjusted ASM was greater than that between the BMDs and weight adjusted ASM.

Table 2. Bivariate Correlations among vitamin D, appendicular skeletal muscle mass and BMDs at various sites.

		Vitamin D	Weight Adjusted ASM	Height Adjusted ASM	Whole body BMD	Lumbar spine BMD	Femoral Neck BMD	Total Femur BMD
	unadjusted		-0.010	0.048**	-0.008	-0.037**	-0.021	0.020
Vitamin D	Adjusted		0.039	0.056*	0.060	0.042	0.066**	0.093**
Weight	unadjusted			0.094**	0.076**	0.033**	0.066**	0.014**
adjusted ASM	adjusted			0.644**	0.124**	0.024	0.082**	0.048*
Height	unadjusted				0.163**	0.187**	0.218**	0.267**
Adjusted ASM	adjusted				0.197**	0.216**	0.246**	0.316**
Wholebody	unadjusted					0.527**	0.495**	0.495**
BMD	adjusted					0.657**	0.602**	0.596**
Lumbar	unadjusted						0.542**	0.537**
spine BMD	adjusted						0.640**	0.662**
Femoral	unadjusted							0.699**
Neck BMD	adjusted							0.859**
Total Femur	unadjusted							
BMD	adjusted							

** : P value <0.01

- : P value <0.05

BMD : Bone mineral denisty

ASM : Appendicular skeletal muscle mass

Adjusted :age, menstrual status, dailycalciumintakeand moderate exercise.

3.3 Influence of Vitamin D on sarcopenia

Woman with vitamin D deficiency had 2.57 times greater odds ratio fortype 2 sarcopenia, compared with woman with sufficient vitamin D level. After adjusted for the multiple variables, the odd ratio went up to 4.72 times. Thoughvitamin D insufficiency hadno significant effect on sarcopenia in unadjusted and multiple variables adjusted model, it did show trend for sarcopenia

Table 3. Unadjusted and adjusted odds ratio ofvitamin D deficiency for sarcopenia.

		Vitamin D level		
		Sufficiency >20 ng/ml (26.7%)	Insufficiency 10-20 ng/ml (63.6%)	Deficiency <10 ng/ml (9.7%)
Odds Ratio for type 2 sarcopenia	Model 1	1 (ref)	1.41 (0.84 – 2.37)	2.57** (1.34 – 5.02)
	Model 2	1 (ref)	1.762* (1.02 – 3.04)	3.90** (1.89 – 8.05)
	Model 3	1 (ref)	1.79 (0.92 - 3.45)	4.72** (2.01 – 11.1)

95% confidence interval was presented in the brackets
Ref : Reference group

** : P value <0.01
- : P value <0.05

Model 1: Unadjusted
Model 2: Adjusted age and BMI
Model 3: Adjustedage, BMI, menstrual status, calciumintakeand moderate exercise

3.4The risk for osteoporosis according to vitamin D deficiency and Sarcopenia

In unadjusted model, relative to women with sufficient vitamin D, women with neither vitamin D insufficiencynor deficiency did not show significant odd ratio for osteoporosis at any site except femoral neck in vitamin D insufficient group.However afteradjusted age, BMI, menstrual status, calciumintakeand moderate exercise , odds ratios for osteoporosis at femoral neck and total femur became significant in women with vitamin D deficiency .

After adjusted for height adjusted ASMas well as other variables, odds ratios remainedsignificant at femoral neck and showed same trend at total femur. Vitamin D insufficiencyor deficiency did not show effects on lumbar BMD in any model.

Table 4. Unadjusted and adjusted odds ratios for osteoporosisin groups with different vitamin D concentration.

		Vitamin D level		
		Sufficient N = 1068	Insufficient N = 2383	Deficient N = 369
Lumbar spine L1-4 osteoporosis	Model 1	1 (ref)	0.77 (0.50 – 1.18)	0.72 (0.34 – 1.52)
	Model 2	1 (ref)	1.22 (0.77 – 1.94)	0.99 (0.44 – 2.23)
	Model 3	1 (ref)	1.27 (0.78 – 2.06)	1.05 (0.45 – 2.45)
	Model 4	1 (ref)	1.26 (0.78 – 2.04)	1.01 (0.43 – 2.37)
Femoral neck osteoporosis	Model 1	1 (ref)	0.58** (0.42 – 0.81)	1.06 (0.65 – 1.71)
	Model 2	1 (ref)	0.92 (0.63 – 1.36)	2.02* (1.11 – 3.70)
	Model 3	1 (ref)	0.99 (0.66 – 1.48)	2.16* (1.13 – 4.12)
	Model 4	1 (ref)	0.98 (0.65 – 1.46)	2.05* (1.07 – 3.92)
Total Femur osteoporosis	Model 1	1 (ref)	0.74 (0.51 – 1.09)	1.24 (0.72 – 2.15)
	Model 2	1 (ref)	1.25 (0.81 – 1.93)	2.14* (1.10 – 4.18)
	Model 3	1 (ref)	1.25 (0.79 – 1.97)	2.19* (1.09 – 4.45)
	Model 4	1 (ref)	1.23 (0.78 – 1.94)	2.01 (1.00 – 4.08)

95% confidence interval was presented in the brackets
Ref : Reference group

** : P value <0.01
- : P value <0.05

Model 1: Unadjusted
Model 2: Adjusted for age and BMI
Model 3: Adjusted for age, BMI, menstrual status, calciumintakeand moderate exercise
Model 4: Adjusted for age, BMI, menstrual status, calciumintakeand moderate exerciseandweightadjusted ASM

Before adjustment, the odds ratios for osteoprosis attotal femur and femoral neckin type 2 sarcopeniawere 2.25 and 2.15 respectively, compared with normal muscle group. After adjustment for the mutiple variables, the odd ratios were 2.71 and 4.29 respectively intype 2 sarcopenia, Even after adjusted for Vitamin D concentration, the relationship between sarcopenia and osteoporosis remained significant.Type 1 sarcopenia showed similar trends wtih type 2 sarcopenia. Both type 1 and type 2 sarcopenia did not show any effects on lumbar BMD.

Table 5. Unadjusted and adjusted odds ratios for osteoporosis in groups classified by weight adjusted ASM

		Weight adjusted muscle mass		
		Normal >28.05% N = 1512	Type 1 sarcopenia 24.23 – 28.05% N = 1911	Type 2 sarcopenia <24.23 % N = 397
Osteoporosis at Lumbar spine	Model 1	1 (ref)	1.46 (0.93 – 2.29)	1.51 (0.73 – 3.12)
	Model 2	1 (ref)	1.46 (0.85 – 2.49)	1.35 (0.57 – 3.22)
	Model 3	1 (ref)	1.51 (0.85 – 2.69)	1.66 (0.67 – 4.10)
	Model 4	1 (ref)	1.50 (0.61 – 3.74)	1.51 (0.84 – 2.67)
Osteoporosis at Femoral Neck	Model 1	1 (ref)	1.38* (1.01 – 1.92)	2.25* (1.41 – 3.58)
	Model 2	1 (ref)	1.61* (1.05 – 2.47)	3.18** (1.66 – 6.09)
	Model 3	1 (ref)	1.56 (1.00 – 2.43)	2.71** (1.35 – 5.41)
	Model 4	1 (ref)	1.57* (1.01 – 2.45)	2.59** (1.29 – 5.21)
Osteoporosis at total femur	Model 1	1 (ref)	1.21 (0.84 – 1.75)	2.15* (1.29 – 3.60)
	Model 2	1 (ref)	1.66* (1.04 – 2.65)	4.10** (2.03 – 8.29)
	Model 3	1 (ref)	1.70* (1.04 – 2.79)	4.29** (2.03 – 9.05)
	Model 4	1 (ref)	1.72* (1.05 – 2.81)	3.96** (1.87 – 8.39)

95% confidence interval was presented in the brackets
Ref : Reference group

** : P value <0.01
- : P value <0.05

Model 1: Unadjusted
Model 2: adjusted for age and BMI
Model 3: adjusted for age, BMI, menstrual status, calciumintakeand moderate exercise
Model 4:adjusted for age, BMI, menstrual status, calciumintakeand moderate exerciseandVitamin D concentration

CHAPTER4. SUMMARY, DISCUSSIONAND CONCLUSION

4.1 Summary of Findings

Both vitamin D concentration and muscle mass positively correlated withBMDsat femoral neck and total femur, but not at lumbar spine. Compared with women with sufficient vitamin D concentration, women with vitamin D deficiency weremore than 2 times likelihood to haveosteoporosisat femoral neck and total femur, independent of influence from muscle mass. Sarcopeniaalso hadnegative impact on BMD like vitamin D deficiency and sarcopenia also has independent effects from vitamin D.

4.2 Discussion

In consistent with our study,a number of cross-sectional studiesincluding Rancho Bernardo's study have reported that serum concentrations of vitamin D were positively related to bone density atproximal femur in the elderly. [12,13] A study [14] including middle-aged women also reported similar relationship between vitamin D concentration and femoral BMD. Supplementation of vitamin D3 for two years in combination with calcium was reported a significant reduction in hip fractures among community dwelling population, resulting in 33% lower rate for osteoporotic fracture and a 22% lower rate for first fracture at any site compared to placebo [15].

Bischoff Ferrari study [16] suggestedthat positive association of serum vitamin D concentration and BMD may be greater in the 90–100 nmol/L (36 - 40ng/L) serum range of vitamin D. Our study indicated that the sufficient level of Vitamin D for BMD can be just above 20ng/ml in Korean population which is pretty lower than in Caucasian population.

Cross-sectional studies showeda positive relationship between vitamin D concentration and muscle mass with aging.In a previous study based on KHNANES, elder Korean men and women with sarcopeniashowed lower 25(OH) D levels, regardless of BMI[17].The longitudinal aging study Amsterdam reported thatlow vitamin D is associated with loss of muscle mass and strength. [18]

Vitamin D has beneficial effects on BMD through promoting muscle mass and contractibility. Vitamin Dreceptor is expressed not only in osteoblast [19] but alsoin myoblast [20]. *In vitro* evidence has demonstrated that vitamin D increases protein synthesis in myoblast and facilitates differentiation of myoblast, resulting in increase in size and number of type 2 muscle fibers [21]. In combination with co-factors ''retinoid X receptor'' and ''Steroid Receptor Coactivator 3'' (SRC), the VDR: $1,25(OH)_2$vitamin D modulates gene expression of a number of proteins, via binding to specific target gene promoter regions, known as ''vitamin D response elements'' (VDRE) [22, 23] results in enhanced transcription of a range of proteins.Calbindin [24],one of proteins induced by vitamin D, plays a role in regulating the membrane calcium channel in skeletal muscle for contractile function, which promotes bone formation. The other is insulin-like growth factor binding protein 3 (IGFBP-3) [22] regulatesaction of insulin like growth factor 1 (IGF-1) thatnot only stimulates terminal differentiation of muscle cells into myotubesbut also promotes stem-cell mediated muscle regeneration and hypertrophy of skeletal muscle. Lean body mass may protect against bone loss, provides greater mechanical loads and stresses than the axial spine through muscular

contraction. Muscle contraction stimulates periosteal apposition, which can also be directly induced by mechanical strain through mechanoreceptors in osteocytes.[25, 26].The beneficial effects of vitamin D on muscle may be explained by moderating secondary hyperparathyroidism which induce atrophy of type 2 muscle fibres in animal models [27]

The Michigan Bone Health Study reported that decreased BMD at the proximal femur could be attributed to premenopausal muscle loss in proximal thigh[28].Another study showed that postmenopausal women with sarcopenia had lower BMD in the femoral neck and total femur. A 12-year longitudinal study [29] showed that reduction in lean body mass contributes to decline in proximal femur BMD. Lean mass is the strongest predictor of cortical bone mineral content of the femur in postmenopausal women [30]but not in the lumbar area. [31]Osteophyticcalcification found in degenerative spondylosis and vascular calcification, usually at the aorta and its major branches can interfere with the interpretation of lumbar BMD and mask the relationship between vitamin D and lumbar spine. [32]. In postmenopausal women the rate of change of bone mineral density, especially at the lumbar spine, may be related to VDR allelic polymorphisms. [33]Observing the change of lumbar-spine bone mineral density over 18 months in 72 elderly subjects, 9 BB homozygotes lost bone mineral density but 26 homozygotes for the alternative genotype (bb) did not (mean change -2.3 [SE 1.0] vs 0.9 [0.7]% per year, $p < 0.05$), irrespective of calcium intake.
The lumbar BMD in the genotype (bb) 26 homozygotes did not decrease (mean change -2.3 [SE10] vs 0.9 [0.7]% per year, $p<0.05$), irrespective of calcium intake. [34] Lumbar vertebrae, which consist primarily of cancellous bone, are more affected by estrogen levels than the femur. In contrast, the femur contains more cortical bone, and has a lower metabolic rate than trabecular bones.

Vitamin D affects bone formation through stimulating osteoblasts differentiation and suppressing osteoblast apoptosis, which is not related with muscle mass.Vitamin D deficiency causes secondary hyperparathyroidism that increases bone resorption leading to decline in BMD. [34] The cytokines IL-1, IL-6 and TNF- α have been shown to regulate bone [35] and evidence from animal models has suggested that cytokines are associated with the development of osteoporosis [36,37] through stimulation of osteoclastogenesis and subsequent bone resorption [38]. Vitamin D level had been more consistently associated with hip BMD than lumbar BMD. [39] Similar results were obtained in a previous study based on KHNANES 2009 -2010 [40]

KHNANESIV is a largepopulation-based National wide study, which can increase the statistical reliability of the results. There is only one ethnicity in our study that we can prevent bias originated from diverse ethnicity. The results of our study were adjusted by the body compositions measured by DXA, that has a privilege in accuracy.
Our study has few limitations.The cross-sectional design in our study is one of them. We did not include the function of skeletal muscle such as strength. However muscle strength well correlates with muscle mass and age which we included in the adjustment.

4.3Conclusion

Though vitamin D and muscle mass share beneficial effects on bone mineral density, they haveindependent influence from each otheron BMD

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