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Association between Seasonal Changes in Vitamin D and Bone Mineral Density

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=Abstract=

Objectives: Vitamin D deficiency, which causes secondary hyperparathyroidism, is considered to be a major contributor to osteoporosis. Because the serum 25-hydroxyvitamin D (25-OHD) level depend on sun exposure and, varies by season, the level of serum 25-OHD in each season at which vitamin D status can lead to changes in bone mineral density (BMD) is not known.

Methods: A total of 2,878 women who underwent periodic health examinations at Ajou University Hospital were included in this study. We measured the serum 25-OHD concentrations using radioimmunoassay and BMDs using dual energy x-ray absorptiometry (DXA). The differences in serum 25-OHD levels among groups as a function of age, season, and BMD were tested by one-way ANOVA.

Results: The serum 25-OHD level was not different based on age, but by season, with higher levels in the summer and autumn than in the winter and spring. However, the 25-OHD level did not have a significant relationship with BMD in any season.

Conclusion: The serum 25-OHD level represents vitamin D status at the time of testing, which is not associated with long-term changes in BMD. When the 25-OHD levels are used to make clinical decisions related to the treatment of osteoporosis, careful interpretation is required. **(J Korean Soc Menopause 2011;17:88-93)**

Key Words: Bone mineral density, Seasonal variation, Vitamin D

Vitamin D deficiency that causes secondary hyperparathyroidism has been considered as a major contributor for osteoporosis.[1~4] Vitamin D is made from food or skin via ultraviolet irradiation.[4~6] Therefore serum vitamin D levels undergo seasonal changes.[2,4,6]

There have been several studies on the association between serum 25-hydroxyvitamin D (25-OHD) levels and bone mineral density (BMD).[7,8] However, most of these studies didn't take seasonal changes into consideration. In addition, there has been little information on 25-OHD and BMD in Koreans. Therefore, we attempted to assess the association of vitamin D status with bone mineral density in Koreans, considering seasonal changes of vitamin D.

Materials and Methods

In Korea, many people take a periodic health examination annually or biannually. A periodic health examination is checking a health status in a hospital. Laboratory tests and checking height and weight are generally included. One can also add bone densitometry as an option in a periodic health examination. We retrospectively investigated the random data of 3,583 women who checked their serum 25-OHD levels and BMD for a periodic health examination at Ajou University Hospital. The study was conducted between January 1999 and March 2005. If one subject had taken a health examination more than twice between January 1999 and March 2005, we

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chose the first health examination data. We excluded 705 subjects who had thyroid diseases or rheumatic diseases and the ones who took medication, which can affect the bone mineral density, including steroid, antithyroid drugs, anti-epileptics, bisphosphonates, calcium and vitamin D supplements, or isoflavone based on subject's self questionnaire. We also excluded subjects whose serum creatinine level was above 2.0 mg/dL. At last, we investigated the data of 2,878 subjects. Checking serum parathyroid hormone (PTH) level was not included in a initial health examination. Therefore we could not see the PTH levels.

The number of men who checked serum 25-OHD levels was too small in contrast to the number of women. Therefore we did not include men's data.

Serum 25-OHD levels were assayed with radioimmunoassay kits (DiaSorin Inc., Stillwater, MN, USA). Bone mineral density was measured by dual energy x-ray absorptiometry (DXA, [GE-lunar, expert-XL, USA]).

Osteoporosis was defined as lowest T-score beneath −2.5 according to the criteria of World Health Organization: Osteopenia was from −2.5 to −1.0 and normal was above −1. Spring was defined as from March through May, summer from June through August, fall from September through November, winter from December through February.

The differences in serum 25-OHD levels among age groups, seasons and osteoporosis groups were assessed by one-way ANOVA. All analyses were performed using SPSS Version 11.5 (SPSS Inc., Chicago, IL, USA).

Table 1. General characteristics (n = 2,878)

Characteristics	Number (%)	Mean ± SD
Height (cm)		155.0 ± 5.1
Weight (kg)		58.5 ± 14.4
Age (yrs)		52.5 ± 6.3
< 40	37 (1.3)	37.6 ± 1.9
40～49	910 (31.6)	46.2 ± 2.5
50～59	1,536 (53.4)	53.9 ± 2.7
60～69	375 (13.0)	62.7 ± 2.4
≥ 70	20 (0.7)	71.8 ± 2.6
Body mass index (kg/m^2)		24.3 ± 6.2
Season		
Spring	748 (26.0)	
Summer	652 (22.7)	
Fall	601 (20.9)	
Winter	877 (30.5)	

Results

1. General characteristics

Mean age of the subjects was 52.5 ± 6.3 years and mean body mass index was 24.3 ± 6.2 kg/m^2. The numbers of subjects were 748 (26.0%), 652 (22.7%), 601 (20.9%) and 877 (30.5%) in spring, summer, fall, and winter, respectively (Table 1).

2. Serum 25−OHD levels in each season

Mean serum 25-OHD levels were 15.8 ± 8.2 ng/mL. The mean serum 25-OHD levels in spring were 12.9 ± 7.0 ng/mL, in summer 19.1 ± 9.3 ng/mL, in fall 19.1 ± 8.3 ng/mL, and in winter 13.5 ± 6.5 ng/mL: Serum 25-OHD levels in summer and fall were significantly higher than those in spring and winter (P = 0.01). No significant difference in serum 25-OHD levels was observed between spring and winter, and summer and fall, respectively (P = 0.90) (Table 2).

3. Serum 25−OHD levels in age groups

There was no significant difference in 25-OHD levels among the age groups (P = 0.639) (Table 3).

4. Serum 25−OHD levels in three groups of BMD in each season

We divided the subjects into normal, osteopenia, and osteoporosis group according to the BMD in the L2-L4 lumbar spines. No significant difference in serum 25-OHD levels was

Table 2. Serum 25-hydroxyvitamin D levels during each season

	Number (%)	Mean ± SD	P value*
Spring (March～May)	748 (26.0)	12.9 ± 7.0^a	0.01
Summer (June～Aug)	652 (22.7)	19.1 ± 9.3^b	
Fall (Sep～Nov)	601 (20.9)	19.1 ± 8.3^b	
Winter (Dec～Feb)	877 (30.5)	13.5 ± 6.5^a	

*P value by analysis of variance, ^{a,b}When the analysis of variance was statistically significant (P < 0.05), all pair-wise comparisons among seasonal groups were tested for statistical significance using the Duncan's multiple comparison test. Pair-wise comparisons that were significantly different from one another are indicated by superscripts as follows; when the values for a column do not share a common superscript, they are significantly different, whereas if the values do share a common superscript, they are not significantly different

observed among three groups (P = 0.618). The BMD in the femoral neck also revealed no significant difference in serum 25-OHD levels among three groups (P = 0.370) (Table 4).

Table 3. Serum 25-hydroxyvitamin D levels in age groups

Age (yr)	N (%)	Mean ± SD	*P* value*
< 40	37 (1.3)	14.6 ± 7.5	
40～49	910 (31.6)	15.6 ± 8.1	
50～59	1,536 (53.4)	16.0 ± 8.1	0.639
60～69	375 (13.0)	15.5 ± 9.1	
≥ 70	20 (0.7)	16.7 ± 8.8	

*P value by analysis of variance

When we divided the subjects into three groups by BMD in L2-L4 lumbar spines, serum 25-OHD levels in the osteoporosis group in the summer were significantly higher than those in the normal and osteopenia groups (P = 0.029). However, in the fall, serum 25-OHD levels were significantly lower in the osteoporosis group than those in the others (P= 0.018). When we divided the subjects into three groups by BMD in femoral neck, serum 25-OHD levels in the osteoporosis group in the summer were higher than those in the other groups with statistical significance (P = 0.014). The serum 25-OHD levels revealed no significant difference among three groups by BMD in both L2-L4 spines and femoral neck in the spring and winter

Table 4. Serum 25-hydroxyvitamin D levels in groups based on classification of osteoporosis

	BMD at L2-L4			BMD at the femoral neck		
	N (%)	Mean ± SD	*P* value*	N (%)	Mean ± SD	*P* value*
Normal	1,740 (60.5)	15.6 ± 7.9		2,137 (74.3)	15.9 ± 8.1	
Osteopenia	861 (29.9)	16.0 ± 8.7	0.618	687 (23.9)	15.4 ± 8.0	0.370
Osteoporosis	277 (9.6)	15.9 ± 8.9		54 (1.9)	16.4 ± 13.3	

*P value by analysis of variance. BMD: bone mineral density

Table 5. Serum 25-hydroxyvitamin D levels in three groups of bone mineral density in each season

	BMD at L2-L4			BMD at the femoral neck		
	N (%)	Mean ± SD	*P*-value*	N (%)	Mean ± SD	*P* value*
Spring						
Normal	437 (58.4)	12.9 ± 7.0		543 (72.6)	13.0 ± 7.1	
Osteopenia	234 (31.3)	12.8 ± 6.7	0.759	186 (24.9)	12.4 ± 6.6	0.428
Osteoporosis	77 (10.3)	13.5 ± 8.0		19 (2.5)	14.1 ± 7.8	
Summer						
Normal	380 (58.3)	18.3 ± 8.6[a]		486 (74.5)	19.0 ± 9.0[a]	
Osteopenia	202 (31.0)	20.0 ± 10.3[a,b]	0.029	155 (23.8)	18.7 ± 8.4[a]	0.014
Osteoporosis	70 (10.7)	20.7 ± 9.4[b]		11 (1.7)	27.1 ± 23.1[b]	
Fall						
Normal	395 (65.7)	18.9 ± 7.8[a]		461 (76.7)	19.2 ± 8.3	
Osteopenia	161 (26.8)	20.3 ± 9.2[a]	0.018	133 (22.1)	18.7 ± 8.3	0.857
Osteoporosis	45 (7.5)	16.5 ± 8.5[b]		7 (1.2)	19.7 ± 10.6	
Winter						
Normal	528 (60.2)	13.6 ± 6.5		647 (73.8)	13.5 ± 6.4	
Osteopenia	264 (30.1)	13.0 ± 5.9	0.422	213 (24.3)	13.5 ± 7.0	0.251
Osteoporosis	85 (9.7)	13.9 ± 7.9		17 (1.9)	10.9 ± 4.8	

*P value by analysis of variance. [a,b]When the analysis of variance was statistically significant (P < 0.05), all pair-wise comparisons among BMD groups were tested for statistical significance using the Duncan's multiple comparison test. Pair-wise comparisons that were significantly different from one another are indicated by superscripts as follows; when the values for a column do not share a common superscript, they are significantly different, whereas if the values do share a common superscript, they are not significantly different. BMD: bone mineral density

(Table 5).

Discussion

The aim of the present study was to assess the association of vitamin D status with bone mineral density in Koreans, considering seasonal variations of vitamin D.

Although 1, 25-OHD, an active form of vitamin D, reflects more actual vitamin D stores, its short half life and low serum concentration make serum 25-OHD as a general indicator of vitamin D stores. Therefore, we measured serum 25-OHD level as an indicator of vitamin D status.

Our results of seasonal changes in serum 25-OHD levels are in agreement with earlier studies: The levels were higher in summer and fall than in spring and winter.[9] In Japanese population, serum 25-OHD levels were highest in September, and lowest in March.[5] No difference was seen in June and December. However, they measured the serum 25-OHD level in only one time, therefore, these results couldn't exactly represent the seasonal serum 25-OHD levels. In addition, the result in June is hard to be regarded as summer vitamin D levels, since the results would have been different, if they had measured in July or August. There has been one earlier study about seasonal variations of vitamin D status in Korean population which was measured only in March and September,[6] however, there has been no study on the changes of vitamin D level throughout four seasons. In our present study, we measured the changes of serum 25-OHD levels during four seasons, and found that the level was high in summer and low in winter. However, no significant difference was seen between summer and fall and also between spring and winter.

There has been contracdictory results about an association of serum 25-OHD level with age. A few studies showed that increasing age diminishes serum 25-OHD levels.[10,11] It is known that the capacity of human skin to produce vitamin D3 decreases in the elderly.[12,13] On the other hand, there was a racial difference in an association of serum 25-OHD levels with age in the large Nutrition Examination Survey III (NHANES III) population.[7] As age increased, serum 25-OHD levels decreased in Whites, whereas rather increased in Blacks. Furthermore, the serum 25-OHD levels were lower in young adult women than in older women in Japanese studies.[5,14] In a recent Korean study, no association was shown between serum 25-OHD level and age in menopausal women.[3] Our study also showed no significant difference in serum 25-OHD levels between the age groups.

Serum 25-OHD levels did not show consistent relationship with osteoporosis groups by BMD. First of all, the BMD in the L2-L4 spines and femoral neck showed similar results. Next we investigated the relationship between the serum levels and BMD by each season, and found that the BMD in the L2-L4 spines indicated the serum levels increased in summer and decreased in fall in the osteoporosis group. The BMD in the femoral neck also indicated that they increased in summer in the osteoporosis group. Nevertheless, no significant association was observed in spring and winter, between the serum 25-OHD levels and BMD in the L2-L4 spines and femoral neck, thus, showing inconsistent relationship between serum 25-OHD levels and the classification of osteoporosis.

In Western countries, several studies reported a positive association between serum 25-OHD levels and BMD.[15~18] Recently, the large Nutrition Examination Survey III (NHANES III) population study in USA observed also similar result.[7] It should be noted that the serum 25-OHD levels in the above study are relatively higher than those in our study. On the contrary, however, a few studies reported a lack of association between serum 25-OHD levels and BMD,[19,20] and in these studies, the serum 25-OHD levels are relatively lower than ours. A recent study of postmenopausal women in France indicated that serum 25-OHD level did not correlate with BMD at the hip and radius after adjustment for age.[8] Several Japanese studies also reported a lack of association between them;[14,21,22] in those studies, the serum 25-OHD levels are almost equal or slightly lower than those in our study. In a Korean study, the difference in BMD between severe vitamin D deficiency and mild deficiency groups and between moderate deficiency group and normal one was significant ($P < 0.05$).[23] However, mean BMD was higher in mild vitamin D deficiency group than in normal group. The mean BMD of severe vitamin D deficiency group was higher than that of moderate vitamin D group. Thus, inconsistent correlation was shown. The mean serum 25-OHD levels of the above study by So and Park are lower than our results.[23] To sum up all these variable results, it is highly possible that serum 25-OHD at above some levels may have a positive association with BMD. However, more investigations are still needed.

The mean serum 25-OHD levels in the NHANES III

population study are higher than those in our study, but the mean BMD is similar to ours. Therefore, it is possible that vitamin D may play a less important role in BMD of Koreans than that of Americans. In order to confirm this suggestion, we need more studies on the factors affecting BMD in Koreans.

One study for 99 Korean postmenopausal women from Bucheon area showed serum 25-OHD level is correlated with age, osteoporosis and duration of menopause.[24] However, the number was too small and seasonal variations were not considered. The serum 25-OHD level was not correlated with osteopenia and normal BMD.

Menopause may affect both the serum 25-OHD level and BMD. The mean menopausal age in Korean women is 50. Therefore, we did the same analysis excluding 947 women before age 50. The result was not different. No significant difference in serum 25-OHD levels was observed among three BMD groups (P = 0.776 in L2-L4 lumbar spines, P = 0.158 in femoral neck).

In Korean women, random serum 25-OHD level does not have an association with BMD, considering seasonal variations of vitamin D. However, this was a cross-sectional study, therefore the results could be different, if we could follow up the subjects for a long time.

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= 국문초록 =

연구목적: 비타민 D 결핍은 이차성 부갑상선 기능항진증을 유발하여 골밀도의 감소를 가져온다. 비타민 D는 자외선에 의해 피부에서 합성되므로 일조량에 따라 계절별로 혈중농도가 달라진다. 이 연구는 어느 계절에 측정된 혈청 25-hydroxy 비타민 D 값이 실제 골밀도와 연관이 있는지 알아보았다.

연구재료 및 방법: 이 연구는 1999년 1월부터 2005년 3월까지 아주대학병원 건강검진센터를 내원한 여성 중 혈청 25-hydroxy 비타민 D와 골밀도를 측정한, 2,878명을 대상으로 하였다.

결　　과: 혈청 25-hydroxy 비타민 D 농도는 봄, 겨울에 비해 여름, 가을에 통계적으로 의미 있게 높았다. 그러나 겨울과 봄 사이 또는 여름과 가을 사이는 혈청 25-hydroxy 비타민 D 농도에 차이가 없었다. 혈청 25-hydroxy 비타민 D 농도는 골밀도에 따른 골다공증 분류와 연관성이 없었다.

결　　론: 혈청 25-hydroxy 비타민 D 농도는 검사 당시 비타민 D 상태는 반영하지만, 이것이 장기적으로 골밀도와 어떤 관련이 있는 지는 분명하지 않으므로 골다공증 진료에서 혈청 25-hydroxy 비타민 D 농도를 이용할 때는 주의가 필요하다.

중심단어: 비타민 D, 골밀도, 계절변화