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Relationship between Vitamin D, Parathyroid Hormone, and Bone Mineral Density in Elderly Koreans

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There is controversy regarding definition of vitamin D inadequacy. We analyzed threshold 25-hydroxyvitamin D (25[OH]D) below which intact parathyroid hormone (iPTH) increases, and examined age- and sex-specific changes of 25(OH)D and iPTH, and association of 25(OH)D and iPTH with bone mineral density (BMD) in elderly Koreans. Anthropometric parameters, serum 25(OH)D and iPTH, lumbar spine and femur BMD by dual-energy radiography absorptiometry (DXA) were measured in 441 men and 598 postmenopausal women. iPTH increased below serum 25(OH) of 36.7 ng/mL in men, but failed to reach plateau in women. Femur neck BMD above and below threshold differed when threshold 25(OH)D concentrations were set at 15-27.5 ng/mL in men, and 12.5-20 ng/mL in postmenopausal women. Vitamin D-inadequate individuals older than 75 yr had higher iPTH than those aged ≤ 65 yr. In winter, age-associated iPTH increase in women was steeper than in summer. In conclusion, vitamin D inadequacy threshold cannot be estimated based on iPTH alone, and but other factors concerning bone health should also be considered. Older people seemingly need higher 25(OH)D levels to offset age-associated hyperparathyroidism. Elderly vitamin D-inadequate women in the winter are most vulnerable to age-associated hyperparathyroidism.

Key Words: Vitamin D; Intact Parathyroid Hormone; Bone Density; Age; Sex

INTRODUCTION

Vitamin D plays an important role in skeletal development and maintenance. Chronic vitamin D inadequacy in adults can result in compensatory hyperparathyroidism, leading to increased bone turnover, enhanced bone loss, and increased risk of fragility fracture. Therefore maintaining appropriate levels of serum 25(OH)D and iPTH is important for bone health (1-3). In addition to its well known skeletal effect, vitamin D plays an important role in maintaining muscle balance and function, as well as inhibiting the development of autoimmune diseases, cancer, heart disease, and cognitive dysfunction (4-7).

Factors that have been reported to be associated with vitamin D inadequacy include skin pigmentation, sunlight exposure, dietary intake, medications, body fat content, and age (4, 8-10). Increased age has especially been associated with lower 25(OH)D levels owing to changes in lifestyle factors such as clothing and decreased outdoor activities, and owing to reduced cutaneous vitamin D synthesis capacity and dietary intake of vitamin D. Whether age *per se* is associated with higher iPTH levels is controversial, but recent investigations have shown that older people require higher levels of serum 25(OH)D compared with younger people to offset compensatory hyperparathyroidism (11, 12). It has also been reported that serum 25(OH)D levels decline with age earlier in women than in men and less efficiently prevent compensatory hyperparathyroidism in older adults (11). However, the association between age and 25(OH)D and iPTH has mostly been studied on populations that include rela-

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tively young individuals and there are not many studies limited to old people.

Though definitions of vitamin D inadequacy vary and several cutoff levels for vitamin D inadequacy have been suggested, it is now generally accepted that serum 25(OH)D concentration of 30 ng/mL* (*Conversion of ng/mL units to nM/L can be accomplished by multiplying the reported serum 25(OH)D value in ng/mL by 2.5.) is the threshold for vitamin D inadequacy (13, 14). This threshold was derived from the 25(OH)D levels at which iPTH levels reach a plateau in many reports. However, iPTH alone is not enough to define the vitamin D inadequacy threshold (15). Studies on the relation between 25(OH)D levels and BMD are necessary to evaluate the actual effects of vitamin D levels on bone health. Moreover, since old people are more prone to secondary hyperparathyroidism due to factors such as decreased intestinal calcium absorption, the vitamin D inadequacy threshold in elderly people should be separately addressed.

In this study, we analyzed the relation between serum 25(OH) D levels, iPTH levels and BMD values in elderly individuals living in a Korean rural community. Age- and sex-related changes of 25(OH)D and iPTH will also be addressed in our study. To our knowledge this would be one of the first large-scale community based study on vitamin D and iPTH levels on elderly Koreans.

MATERIALS AND METHODS

Study subjects

Study subjects were participants of the Catholic Metabolic disease Cohort (CMC) Study (16). The Catholic Metabolic disease Cohort Study is a longitudinal cohort study which began in 2003, based in the Chungju suburb community. Chungju is a city located in the center of the Korean Peninsula, in North Chungcheong province, at latitude 36.6 north. Through the stratified cluster sampling method, 1/4 of inhabitants aged 40 yr and over was recruited annually from each suburban area in Chungju. We performed a cross-sectional evaluation of the results of 1,069 ambulatory individuals aged 50 yr and over who participated the Catholic Metabolic disease Cohort Study from May 2007 until February 2008. Individuals were excluded who had creatinine clearance values less than 30 mL/min according to the Cockcroft-Gault equation* (*Cockcroft-Gault equation: creatinine clearance = [140-age] × [Wt in kg] × [0.85 if female]/[72 × Cr]), who had underlying chronic kidney disease or thyrotoxicosis or current cancer at the time of the investigation, who had used steroids for more than 3 consecutive months, who had been treated with bisphosphonates or selective estrogen receptor modulators or estrogen hormone or calcitonin, or who did not have adequate blood samples for measurement of 25(OH)D. Women who were in the premenopausal or perimenopausal state, or who had a history of bilateral oophorectomy were excluded. Menopause was defined as the absence of menstruation for at least 12 months.

Clinical evaluation

Information regarding past medical history, past fracture history, family history of fracture, current and prior medication use, exercise (≥ 3 times per week vs < 3 times per week), smoking (yes or no), alcohol drinking (≥ 4 times per week vs < 4 times per week) and educational attainment was collected. Education attainment was categorized as less than elementary education, elementary school graduate, middle school graduate, high school graduate, and college graduate. Dietary calcium intake was assessed with a previously validated food-frequency questionnaire (FFQ) which used the 3-day diet record method (17).

BMD measurement

BMD of the lumbar spine (L1-4) and femur was measured using DXA (Hologic DQR 4500, Waltham, USA) by a single technician. Body mass index (BMI) was calculated by dividing body weight (kg) by the square of body height (m^2). The coefficients of variation (CVs) of the BMD measurements were 1.36% for the lumbar spine and 1.5% for the total femur.

Biochemical measurements

A 12-h-fasting blood specimen was drawn from each individual. Serum was stored at -70°C within 30 min of blood draw. Serum 25(OH)D concentration was measured with the Liaison® TOTAL chemiluminescent immunoassay (CLIA) (DiaSorin, Stillwater, Minnesota, USA) which has an inter-assay CV value of 6.3% and an intra-assay CV value of 2.9%. The limit of detection was 4.0 ng/mL and the reference range was 4.8-52.8 ng/mL. Since there are large interlaboratory differences in assays for serum 25(OH)D (18, 19), serum 25(OH)D levels were measured with both the Diasorin Liaison® TOTAL CLIA and Diasorin radioimmunoassay (RIA) (DiaSorin, Stillwater, Minnesota, USA, intra- and inter-assay CV: 4.0% and 5.3% respectively) for interassay comparison in 100 individuals who were randomly selected in an age- and sex-matched method from the cohort. The serum iPTH concentration was measured with the Liaison® N-tact™ PTH Assay (DiaSorin, Stillwater, Minnesota, USA), which has an intra- and interassay CV of 3.7% and 3.5%, respectively. All biochemical measurements were performed in a central laboratory (Neodin Medical Laboratories, Seoul, Korea) for accuracy and consistency.

Statistical analyses

Pearson's product moment correlation coefficient was used to assess correlations between continuous variables. Partial correlation analysis was performed to adjust for confounding factors. Student's t-test was used to test a difference in two mean values. One-way analysis of variance (ANOVA) with Tukey's or Dun-

nett's multiple comparison was used to test differences among multiple mean values. An analysis of covariance (ANCOVA) was performed to test for differences in mean values while adjusting for cofactors. A probability value of $P < 0.05$ was taken as statistically significant. All statistical analyses were performed using SPSS Version 15.0 and SAS Version 9.1 for Windows software (SAS Institute Inc., Cary, NC, USA).

Ethics statement

This study was approved by the institutional review board at Seoul St. Mary's hospital (KCMC070T076) and informed consent was obtained from all participants.

RESULTS

Baseline characteristics

The sex-specific baseline characteristics of the participants are shown in Table 1. The study population comprised 441 (42.4%) men and 598 (57.6%) postmenopausal women. Seventy-two point six percent of men and 80.1% of women were in their sixties and seventies resulting in no significant difference between the mean ages of the two genders. Eighty point two percent of men and 61.7% of women were farmers, respectively. Sixty-seven point one percent of men and 92.2% of women received less than middle school education. Twenty-nine point nine percent of men took alcohol 4 times or over per week whereas only 2% of women drank such amounts. Thirty-two point seven percent of men and 4.6% of postmenopausal women were smokers, respectively. The mean serum 25(OH)D concentration was 21.6 ± 7.4 ng/mL in men and 16.6 ± 5.9 ng/mL in postmenopausal women.

Association between 25(OH)D and iPTH

25(OH)D had a negative correlation with iPTH in men (r = -0.249, $P < 0.001$) and women (r = -0.228, $P < 0.001$), respectively. The values for vitamin D and iPTH were plotted on a scatter plot for each sex, and the exponential decay model was used to assume the 25(OH)D level at which iPTH concentrations theoretically attain the plateau value. The 25(OH)D and iPTH concentrations for each sex were fit to a three-parameter exponential decay function using the approach used by Chapuy et al. (19). The resulting exponential decay formulas were as follows:

iPTH (pg/mL)
= 39.2 + 47.9 exp (-0.08 × 25[OH]D [ng/mL]) (men)
iPTH (pg/mL)
= 22.6 + 46.0 exp (-0.03 × 25[OH]D [ng/mL]) (women)

With this approach, the iPTH concentration reached a theoretical plateau at 41.6 pg/mL and the corresponding 25(OH)D level was 36.7 ng/mL in men. In women, the exponential decay function failed to identify a plateau for serum iPTH (Fig. 1). Twelve of the 441 men (2.7%) had 25(OH)D levels equal to or above 36.7 ng/mL.

Association of 25(OH)D and iPTH with BMD

Partial correlation analysis was performed to analyze the relation between 25(OH)D and iPTH with BMD with adjustment

Table 1. Demographics, serum biochemical profiles, physical performance measures, and bone mineral density of study subjects

Parameters	Men (n = 441)	Postmenopausal women (n = 598)	*P* value
25(OH)D (ng/mL)*	21.6 ± 7.4	16.6 ± 5.9	< 0.001
Parathyroid hormone (pg/mL)†	49.2 ± 21.9	51.7 ± 23.4	0.065
Age (yr)	66.2 ± 9.1	67.5 ± 7.5	0.025
Height (cm)	164.3 ± 5.9	150.3 ± 5.6	< 0.001
Weight (kg)	61.6 ± 9.4	54.2 ± 8.5	< 0.001
BMI (kg/m^2)	22.8 ± 3.0	24.0 ± 3.2	< 0.001
BMD of lumbar spine (g/cm^2)	0.893 ± 0.166	0.726 ± 0.137	< 0.001
BMD of total femur (g/cm^2)	0.889 ± 0.127	0.719 ± 0.120	< 0.001
BMD of femoral neck (g/cm^2)	0.745 ± 0.126	0.591 ± 0.114	< 0.001
Exercise ≥ 3 times per week, n (%)	30 (6.0)	46 (7.2)	0.406
Alcohol intake ≥ 4 times per week, n (%)	149 (29.9)	13 (2.0)	< 0.001
Current smoker, n (%)	163 (32.7)	29 (4.6)	< 0.001
Calorie intake (kcal/day)	1,499.5 ± 415.0	1,374.6 ± 325.3	< 0.001
Calcium intake (mg/day)	298.3 ± 182.8	289.7 ± 188.7	0.471
Personal history of fragility fracture, n (%)	41 (8.2)	102 (16.1)	< 0.001
Family history of fracture, n (%)	39 (7.8)	45 (7.1)	0.404
Faller, n (%)	54 (10.8)	124 (19.5)	< 0.001
Calcium (mg/dL)	9.5 ± 0.6	9.5 ± 0.6	0.732
Phosphorus (mg/dL)	3.5 ± 0.5	3.9 ± 0.5	< 0.001
Albumin (mg/dL)	4.8 ± 0.4	4.7 ± 0.3	0.009
Creatinine clearance (mL/min)	69.4 ± 17.9	64.6 ± 17.5	< 0.001

Continuous variables were compared using unpaired T-test; categorical variables were compared using Chi-square test. Data are expressed as mean ± SD. *To convert results to SI units: ng/mL × 2.5 = nM/L; †To convert results to SI units: pg/mL × 0.106 = pM/L.

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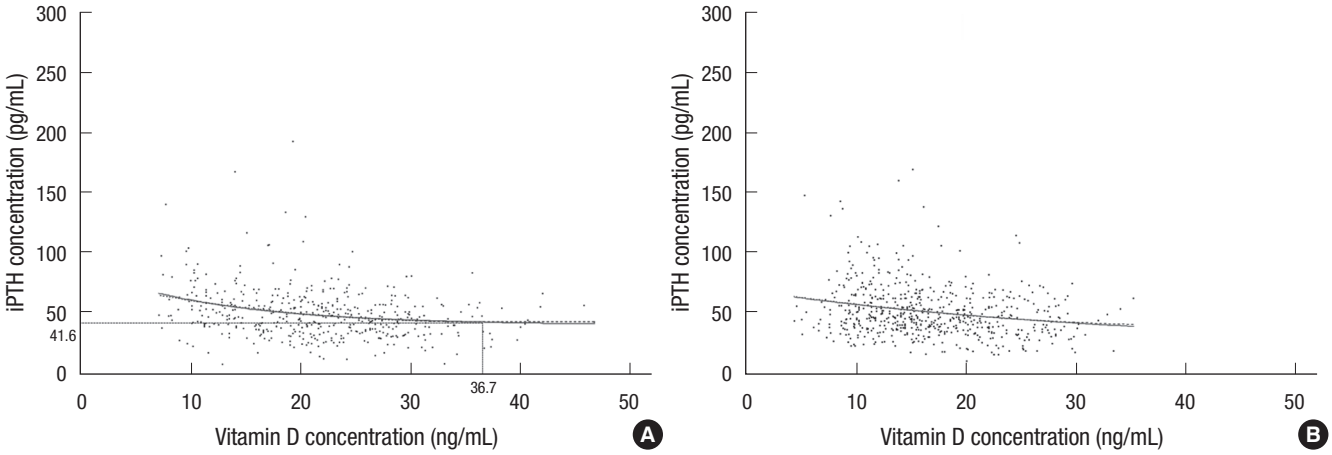

Fig. 1. Relationship between serum (iPTH) and 25-hydroxyvitamin D (25(OH)D) values in men (**A**) and postmenopausal women (**B**). For a 25(OH)D concentration higher than 36.7 ng/mL, there is a plateau level at 41.6 pg/mL for iPTH in men. In women, the exponential decay function failed to identify a plateau for serum iPTH.

Table 2. Correlation analysis between iPTH, 25(OH)D, and BMD values with and without adjustment (Adjustment was performed for age, height, weight, and creatinine clearance)

Parameters	25(OH)D		iPTH	
	r	*P* value	*r*	*P* value
Before adjustment				
Men (n = 441)				
25(OH)D			-0.249	< 0.001
iPTH	-0.249	< 0.001		
Lumbar spine BMD	-0.020	0.665	-0.003	0.941
Femur neck BMD	0.169	< 0.001	-0.107	0.021
Postmenopausal women (n = 598)				
25(OH)D			-0.228	< 0.001
iPTH	-0.228	< 0.001		
Lumbar spine BMD	0.025	0.539	-0.085	0.037
Femur neck BMD	0.086	0.035	-0.091	0.026
After adjustment				
Men (n = 441)				
25(OH)D			-0.244	< 0.001
iPTH	-0.244	< 0.001		
Lumbar spine BMD	-0.006	0.897	0.007	0.889
Femur neck BMD	0.161	0.001	-0.104	0.027
Postmenopausal women (n = 598)				
25(OH)D			-0.229	< 0.001
iPTH	-0.229	< 0.001		
Lumbar spine BMD	0.063	0.126	-0.068	0.098
Femur neck BMD	0.143	< 0.001	-0.030	0.468

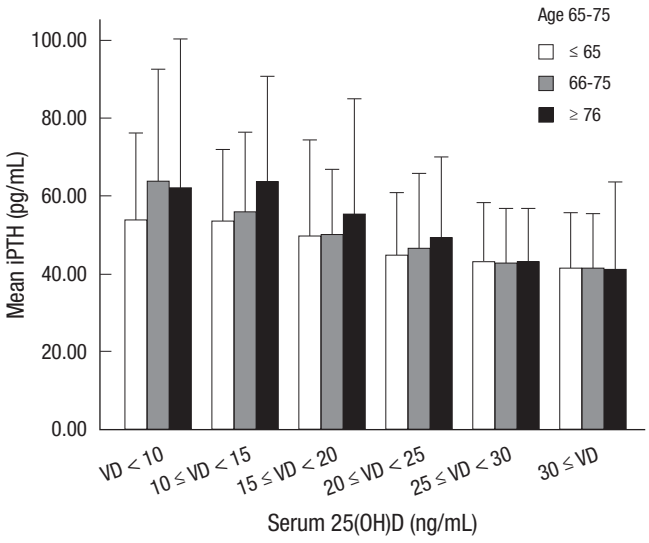

Fig. 2. Serum parathyroid hormone (PTH) levels according to 25(OH)D levels in different age groups. Mean iTPH in individuals older than 75 yr were consistently higher than that of those aged 65 yr or younger, except in the lowest (25(OH)D < 10 ng/mL) vitamin D group (ANOVA, Dunnett's multiple comparison test).

for age, height, weight, and creatinine clearance. Lumbar spine BMD had no significant correlation with either 25(OH)D or iPTH in both men and women after adjustment for age, height, weight, and creatinine clearance. Femur neck BMD was positively correlated with 25(OH)D in both men (r = 0.161, P = 0.001) and women (r = 0.143, P < 0.001) after adjustment. Femur neck BMD also negatively correlated with iPTH both in men (r = -0.104, P = 0.027) and women (r = -0.030, P = 0.468) after adjustment, though this did not reach statistical significance in women (Table 2).

For every 2.5 ng/mL increment in 25(OH)D concentrations, iPTH and femur neck BMD values were compared around the specific 25(OH)D values from 10 ng/mL to 30 ng/mL with adjustment for age, height, weight, and creatinine clearance. There were significant differences between femur neck BMD values when the cut off 25(OH)D concentrations were 15-27.5 ng/mL in men, and 12.5-20 ng/mL in postmenopausal women. The coefficient of determination was greatest in both sex when 25(OH)D concentration was 15 ng/mL (R^2 = 0.279 in men, R^2 = 0.387 in postmenopausal women) (Tables 3, 4).

iPTH and lumbar spine and femur neck BMDs were compared among men who had 25(OH)D levels ≥ 36.7 ng/mL and < 36.7 ng/mL. There were no statistically significant differences in iPTH levels, lumbar spine BMD, and femur neck BMD values (data not shown).

Table 3. Mean femur neck BMD around serum 25(OH)D levels of 2.5-ng/mL increments in men

25(OH)D values	Mean femur neck BMD	*P* value	R^2
< 10 mg/mL (n = 19) ≥ 10 mg/mL (n = 422)	0.703 (0.730*) 0.738 (0.737*)	0.212 (0.945*)	0.252
< 12.5 mg/mL (n = 55) ≥ 12.5 mg/mL (n = 386)	0.698 (0.713*) 0.742 (0.740*)	0.010 (0.075*)	0.257
< 15 mg/mL (n = 94) ≥ 15 mg/mL (n = 347)	0.688 (0.698*) 0.750 (0.747*)	< 0.001 (< 0.001*)	0.279
< 17.5 mg/mL (n = 135) ≥ 17.5 mg/mL (n = 306)	0.712 (0.717*) 0.748 (0.746*)	0.004 (0.008*)	0.264
< 20 mg/mL (n = 180) ≥ 20 mg/mL (n = 261)	0.720 (0.723*) 0.749 (0.747*)	0.011 (0.018*)	0.261
< 22.5 mg/mL (n = 248) ≥ 22.5 mg/mL (n = 193)	0.727 (0.729*) 0.749 (0.747*)	0.060 (0.049*)	0.257
< 25 mg/mL (n = 306) ≥ 25 mg/mL (n = 135)	0.730 (0.730*) 0.753 (0.753*)	0.055 (0.032*)	0.259
< 27.5 mg/mL (n = 344) ≥ 27.5 mg/mL (n = 97)	0.731 (0.730*) 0.760 (0.763*)	0.035 (0.006*)	0.264
< 30 mg/mL (n = 390) ≥ 30 mg/mL (n = 51)	0.734 (0.734*) 0.760 (0.759*)	0.137 (0.115*)	0.256

*Adjusted for age, weight, height, and creatinine clearance.

Table 4. Mean femur neck BMD around serum 25(OH)D levels of 2.5-ng/mL increments in postmenopausal women

25(OH)D values	Mean femur neck BMD	*P* value	R^2
< 10 mg/mL (n = 75) ≥ 10 mg/mL (n = 523)	0.579 (0.573*) 0.590 (0.592*)	0.407 (0.104*)	0.376
< 12.5 mg/mL (n = 171) ≥ 12.5 mg/mL (n = 427)	0.575 (0.570*) 0.595 (0.597*)	0.055 (0.001*)	0.384
< 15 mg/mL (n = 262) ≥ 15 mg/mL (n = 336)	0.579 (0.574*) 0.597 (0.601*)	0.055 (< 0.001*)	0.387
< 17.5 mg/mL (n = 358) ≥ 17.5 mg/mL (n = 240)	0.585 (0.580*) 0.596 (0.603*)	0.237 (0.002*)	0.377
< 20 mg/mL (n = 425) ≥ 20 mg/mL (n = 173)	0.586 (0.584*) 0.598 (0.602*)	0.278 (0.024*)	0.373
< 22.5 mg/mL (n = 488) ≥ 22.5 mg/mL (n = 110)	0.588 (0.587*) 0.597 (0.598*)	0.449 (0.252*)	0.375
< 25 mg/mL (n = 532) ≥ 25 mg/mL (n = 66)	0.587 (0.588*) 0.608 (0.603*)	0.156 (0.198*)	0.375
< 27.5 mg/mL (n = 563) ≥ 27.5 mg/mL (n = 35)	0.588 (0.588*) 0.617 (0.608*)	0.232 (0.216*)	0.375
< 30 mg/mL (n = 589) ≥ 30 mg/mL (n = 9)	0.589 (0.589*) 0.597 (0.580*)	0.843 (0.765*)	0.374

*Adjusted for age, weight, height, and creatinine clearance.

Association between CLIA and RIA

Serum 25(OH)D concentrations were measured with both the Diasorin Liaison® TOTAL CLIA and Diasorin RIA method in 100 subjects randomly selected in an age- and sex-matched method to represent the whole cohort. There was a good correlation between 25(OH)D levels measured with the CLIA and the RIA method ($r = 0.920$, $P < 0.001$). Serum 25(OH)D levels measured with the CLIA method were lower by an average of 5.6 ng/mL compared to levels measured with the RIA method according to the Bland-Altman method.

Associations of Serum 25(OH)D and iPTH levels in relation to age and sex

To compare iPTH levels between old and young individuals with similar 25(OH)D levels, patients were grouped according to 25(OH)D levels by the increment of 5 ng/mL and were further grouped into 3 age categories in each 25(OH)D group. Mean iPTH levels were compared across the age groups in each 25(OH)D group (ANOVA, Dunnett's multiple comparison test). Though the results did not reach statistical significance, mean iTPH in individuals older than 75 yr were consistently higher than that of those aged 65 yr or younger when 25(OH)D levels were within the inadequacy range (Fig. 2).

Age- and sex-specific changes in 25(OH)D and iPTH levels by seasons

Subjects were divided into those who had blood tests in the winter season (September-February) and the summer season

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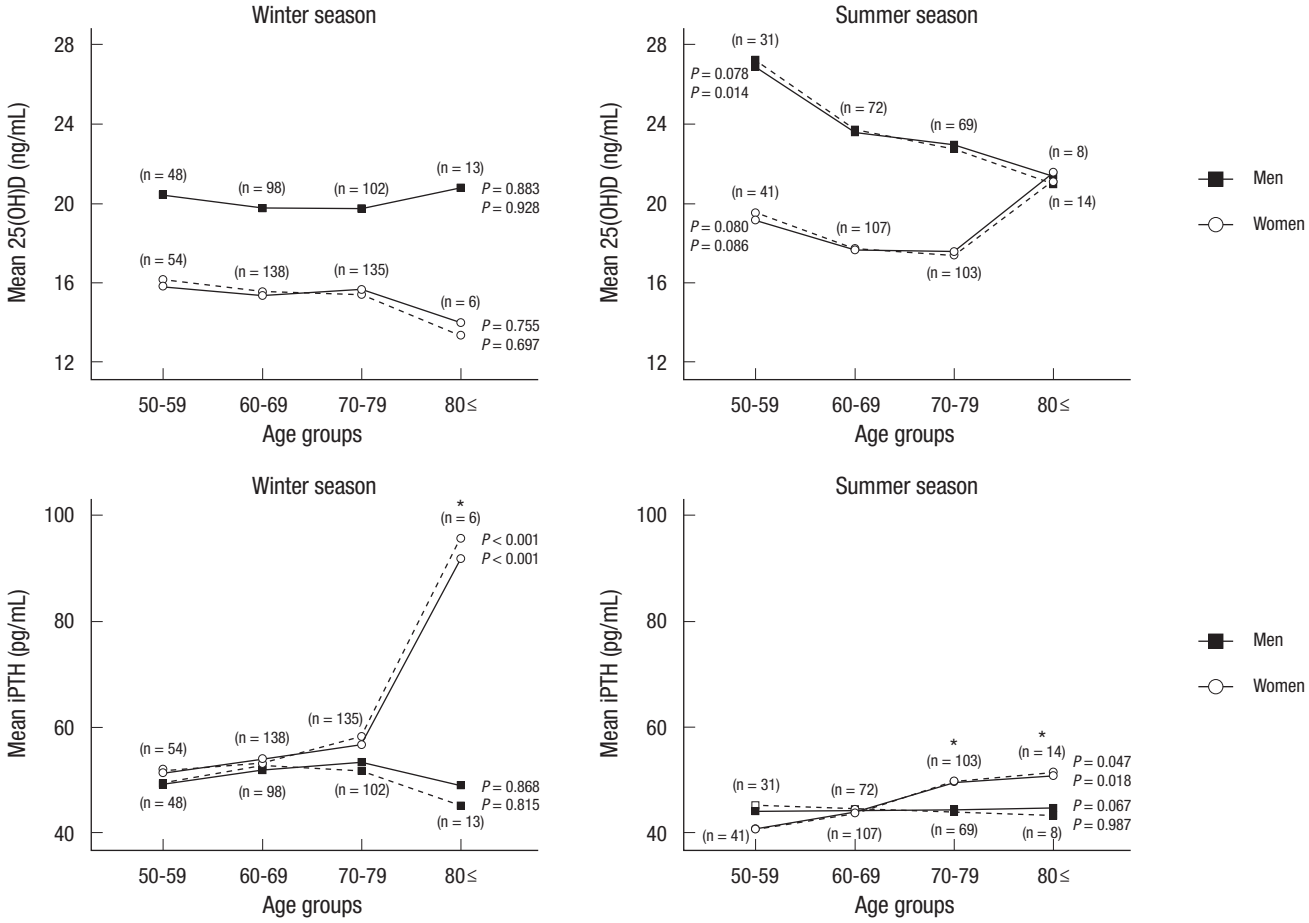

Fig. 3. Mean serum 25(OH)D and iPTH levels according to season and age in men and women. iPTH levels increased significantly in women aged ≥ 80 yr ($P < 0.001$) and ≥ 70 yr ($P = 0.018$) in the winter and summer seasons, respectively. iPTH levels increased significantly in women aged ≥ 80 yr ($P < 0.001$; $P < 0.001$ after adjustment for creatinine clearance and BMI) and ≥ 70 yr ($P = 0.018$; $P = 0.043$ after adjustment for creatinine clearance and BMI) in the winter and summer seasons, respectively. Black boxes indicate men and blank circles indicate women; Dashed lines indicate mean values adjusted for BMI and creatinine clearance; Numbers in squared brackets indicate numbers of men and numbers in round brackets indicates numbers of postmenopausal women, respectively (ANOVA, Dunnett's multiple comparison test, ANCOVA, Bonferroni's multiple comparison).

(May-August), respectively. Serum 25(OH)D levels were significantly lower and serum iPTH levels significantly higher in the winter season compared with the summer season in both men (25[OH]D, 19.97 ± 7.19 vs 24.05 ± 7.04 ng/mL, $P < 0.001$; iPTH 52.01 ± 23.74 vs 43.85 ± 14.53 pg/mL, $P < 0.001$) and women (25[OH]D, 15.58 ± 5.36 vs 18.06 ± 6.44 ng/mL, $P < 0.001$; iPTH, 52.01 ± 23.74 vs 43.85 ± 14.53 pg/mL, $P < 0.001$), respectively. Men and women were further subcategorized by age (decades) in each season and mean 25(OH)D and iPTH levels were compared among decades. 25(OH)D levels were lower in women than in men in most age groups both in the winter and summer seasons. There were no differences in 25(OH)D levels among different age groups in both men and women in the winter season. However, in the summer season, there was a significant progressive decrease in 25(OH)D levels with age in men but no significant difference in women. iPTH levels were significantly higher in women aged ≥ 80 yr ($P < 0.001$; $P < 0.001$ after adjustment for creatinine and BMI) and ≥ 70 yr ($P = 0.018$; $P = 0.047$ after adjustment for creatinine and BMI) in the winter and summer seasons, respectively (ANOVA, Dunnett's multiple comparison test; ANCOVA, Bonferroni's multiple comparison). On the contrary, there were no differences in iPTH levels among across decades in men both in the winter and the summer seasons (Fig. 3).

DISCUSSION

Recent influential reviews have stated that a serum 25(OH)D level of 30 ng/mL should be used as the threshold for vitamin D inadequacy. In the study analyzed in those reviews, serum iPTH showed a plateau at serum 25(OH)D of approximately 30 ng/mL. However, recent studies show that the 25(OH)D level at which iPTH levels attain a plateau cannot be used by itself to estimate the vitamin D inadequacy threshold (15). There are also studies that showed no iPTH plateau in the 25(OH)D-iPTH relation, which makes the choice of an optimal 25(OH)D concentration

based only on iPTH arbitrary (14, 15). Moreover, since results from recent studies suggest relatively higher iPTH levels in old people, it would be necessary to separately address the 25(OH)-iPTH relation in the elderly (15).

Using the exponential decay model to describe the 25(OH)D-iPTH relationship in our study, iPTH levels reached a plateau when 25(OH)D concentration was 36.7 ng/mL in men and iPTH levels failed to reach a plateau in women. The 25(OH)D concentration of 36.7 ng/mL in men far exceeds the consensus threshold for vitamin D inadequacy. When femur neck BMD values around 36.7 ng/mL were compared in men, there were no differences. This may partly be attributable to the small number of men with 25(OH)D levels ≥ 36.7 ng/mL, but further results from our study suggest otherwise.

When femur neck BMD values were compared around specific 25(OH)D values from 10 ng/mL to 30 ng/mL, femur neck BMD values differed when the cut off 25(OH)D concentrations were 15-27.5 ng/mL in men. Also, in postmenopausal women, femur neck BMD values were different when they were compared around 25(OH)D concentrations of 12.5-20 ng/mL. The coefficient of determination was greatest in both sex when 25(OH)D concentration was 15 ng/mL.

Our results show that the threshold vitamin D value cannot be determined in the context of iPTH levels alone, and that the adequate 25(OH)D levels should also be evaluated in the context of other factors concerning bone health, such as BMD. In order to further determine the threshold vitamin D level, measurements on bone turnover markers, and intestinal calcium and phosphorus absorption should also be performed.

Though lumbar spine BMD did not correlate with 25(OH)D and iPTH levels, femur neck BMD was positively correlated with 25(OH)D and negatively correlated with iPTH, in both men and women. (However, femur neck BMD values did not have a statistically significant correlation with iPTH levels in women.) Similar associations have been reported in other studies (20, 21). Degenerative changes in the lumbar spine, aortic and extraskeletal calcification associated with aging may falsely elevate lumbar spine BMD and hence result in a non-specific association between 25(OH)D and lumbar spine BMD (22). Also, it is known that iPTH-mediated bone resorption preferentially involves cortical bone than trabecular bone. Since the femur contains more cortical bone, it is likely that elevated iPTH levels secondary to decreased serum 25(OH)D concentrations may have affected the femur more than the spine.

When study subjects were categorized into 3 age groups and iPTH concentrations were compared among those who had similar 25(OH)D levels, iPTH concentration of the oldest age group was consistently higher than that of younger age groups. This probably implies that older people need higher 25(OH)D levels to offset age-associated hyperparathyroidism. These results are in line with data from women in our cohort.

Older women had higher iPTH levels compared with younger women throughout the year though vitamin D levels were not significantly different among the age groups. The rise in iPTH level was most prominent in women aged ≥ 80 yr in the winter season, which may have been attributable to the especially lower levels of serum 25(OH)D in this season caused by less sunshine exposure.

Similar results have been obtained in other studies (13, 14), but these studies included young individuals, and age-related changes of 25(OH)D and iPTH levels limited to old people have not been evaluated so far. This study excluded individuals aged less than 50 yr, thus giving a perspective into 25(OH)D and iPTH levels in old people. Our results also suggest that older women may be less efficient at preventing secondary hyperparathyroidism caused by low 25(OH)D levels, compared with men and younger women.

Some studies have shown that intestinal calcium absorption decreases with aging, probably due to intestinal resistance to $1,25(OH)_2D$, which leads to compensatory increases in iPTH secretion and 1,25(OH)D production, to maintain calcium absorption and serum ionic calcium (23, 24). Such factors may have contributed to the relatively high iPTH levels in the older individuals in our study. Also, the higher iPTH levels in older women in the winter season may be attributable to the fact that these women had the lowest 25(OH)D levels among all the study subjects. The low 25(OH)D levels, in turn, would have probably resulted from the limited outdoor activities of old women compared to the rest of the individuals in the winter season. Since there were relatively small numbers of individuals aged ≥ 80 yr, more study subjects would be required to further evaluate this phenomenon.

There are some limitations in our study that should be acknowledged. The cross-sectional design of our study limits any causal inferences. Also, our study was performed on very old people dwelling in a rural area and whose educational and economical statuses were very poor. Therefore the results of our study cannot be extended to the general population. However, this study was performed on a relatively large population, and the exclusion of young people from the study allowed the authors to focus on age-related changes of serum 25(OH)D and iPTH in elderly people, and to assess the correlation between 25(OH)D and iPTH with BMD in such a population.

In conclusion, this study shows that the desirable level of serum 25(OH)D cannot be estimated based on iPTH alone, and that other factors concerning bone health, such as BMD, should also be considered to evaluate the optimal level of vitamin D. This study also shows that older people have higher iPTH levels compared with younger people with similar 25(OH)D levels. Therefore older people would require higher levels of 25(OH)D to offset age-related compensatory hyperparathyroidism. This phenomenon was most prominent in the oldest women in our cohort, especially in the winter season, which implies that elder-

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ly vitamin D-inadequate women in the winter are most vulnerable to age-associated hyperparathyroidism.

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