Vitamin D Deficiency with High Intact PTH Levels is More Common in Younger than in Older Women: A Study of Women Aged 39–64 Years

Takeshi Miyamoto,¹ Eri Katsuyama,¹ Hiroya Kanagawa,¹ Atsuhiko Fujie,¹ Hiroya Miyamoto,¹ Shigeyuki Yoshida,² Tomoaki Mori,¹ Kana Miyamoto,¹ Yuiko Sato,¹ Tami Kobayashi,¹ Masaya Nakamura,¹ Morio Matsumoto,¹ Yuji Nishiwaki,⁴ Hiroshi Hirose,³ Takeshi Kanda,³ Ikuo Saito³ and Yoshiaki Toyama¹

¹Department of Orthopedic Surgery, Keio University School of Medicine, Tokyo, Japan

²Department of Dentistry and Oral Surgery, Keio University School of Medicine, Tokyo, Japan

³Health Center and Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

⁴Department of Environmental and Occupational Health, School of Medicine, Toho University, Tokyo, Japan

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Low serum 25-hydroxyvitamin D (25(OH)D) levels are implicated as a risk factor for hip and spine fractures. Studies of the relation between 25(OH)D levels and fractures have primarily involved elderly osteoporosis patients or patients with fractures; however, the serum 25(OH)D and parathyroid hormone (PTH) status in younger adult populations remains largely unknown. We evaluated serum 25(OH)D and intact PTH levels in 411 women aged 39–64 years who were not receiving medication for osteoporosis or other bone diseases. Serum 25(OH)D levels were positively correlated with age ($P = 0.019$), whereas intact PTH levels were inversely correlated with 25(OH)D levels ($P < 0.001$). Thus, low vitamin D levels with high intact PTH levels were more common in younger than in older women. Our data show that serum 25(OH)D insufficiency could be a more serious concern in the younger population than had been previously anticipated. Because serum 25(OH)D insufficiency is reportedly a risk factor for hip and spine fracture, the number of fracture patients could increase in the future, suggesting that we may need to correct the serum vitamin D/intact PTH status to prevent future osteoporosis. (doi: 10.2302/kjm.2015-0010-OA; Keio J Med 65 (2) : 33–38, June 2016)

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Introduction

Osteoporosis leads to hip and spine fractures, often resulting in serious limitation of activities of daily living and reduced quality of life. Fractures also reduce lifespan,¹ indicating that their prevention in osteoporosis patients is crucial. Lower than normal serum 25(OH)D levels have been reported in patients with hip or spine fractures, and vitamin D insufficiency was suggested to be a fracture risk factor.^{2–5} Low vitamin D levels have

also been reported for the elderly population in general and for nonfracture patients.^{6,7} Vitamin D levels are inversely correlated with PTH levels; consequently, vitamin D insufficiency leads to an increase in PTH levels.⁸ Although intermittent PTH infusion promotes increased osteoblastic activity and increased bone mass,⁹ continuous high PTH levels result in increased bone resorption and bone loss.^{8–10} Therefore, it is considered crucial to maintain normal or physiological levels of PTH to prevent osteoporosis. Because serum PTH and 25(OH)D

Table 1 Characteristics of the 411 subjects enrolled in the study

	Mean	SD
Age (years)	48.18	6.63
Height (cm)	157.92	21.62
Weight (kg)	53.94	8.12
BMI (kg/m ²)	21.62	2.99
25(OH)D (ng/ml)	24.63	7.38
Intact PTH (pg/ml)	52.55	16.76
Ca (mg/dL)	9.17	0.29
Cr (mg/dL)	0.64	0.087
TRACP5b (mU/dL)	269.61	110.54
BMD: T score (% YAM)	87.98	15.06
BMD: Z score (% Age matched)	100.36	18.46

YAM, young adult mean; BMD, bone mineral density.

levels are inversely correlated,⁸ correction of low vitamin D levels may counteract high PTH levels. Indeed, serum vitamin D sufficiency is reportedly associated with low incidences of limb and vertebral fractures in elderly women,¹¹ further suggesting that serum vitamin D status is closely related to fracture risk. However, since these studies have been conducted primarily in elderly patients or patients with fractures, most of whom were more than 70 years old, the serum vitamin D status in younger women remains largely unknown. In the current study, we examined serum 25(OH)D and intact PTH levels in women aged between 39 and 64 years who had undergone medical examinations but had not been treated with any osteoporosis-related medications.

Methods

Subjects

The subjects were women aged 39–64 years who were employed by Keio University School of Medicine and had undergone medical examinations in September 2011. All blood samples were collected in September 2011. The subjects included medical doctors, physical and occupational therapists, pharmacists, nurses, and office workers, among others. The study was approved by the Ethics Committee of Keio University School of Medicine. Informed consent was obtained from all subjects.

Measurements

Height, weight, serum 25(OH)D, and intact PTH levels were measured in all subjects. BMI was calculated from the height and weight data. Serum 25(OH)D levels were evaluated using a 125I RIA kit (DiaSorin, Stillwater, MN, USA), and intact serum PTH levels were measured using an kit (Cobas, Roche Diagnostics, Basel, Switzerland).

Bone mineral density was analyzed using a CM-200 bone densitometer (Furuno, Nishinomiya, Hyogo, Japan).

Statistical analysis

Data are presented as means $\pm$ SDs. Statistical and regression analyses were performed using SPSS statistical software (SPSS, Chicago, IL, USA). Pearson's correlation coefficients were calculated for simple regression to evaluate linear relationships between study parameters. Multiple regression analysis was undertaken to evaluate whether serum 25(OH)D levels were independently and significantly associated with intact PTH levels. $P < 0.05$ was considered significant.

Results

A significant proportion of subjects younger than 64 years of age had vitamin D insufficiency

In total, 571 female medical workers who had undergone a medical examination were invited to participate in this study. Informed consent was obtained from 525, 91.94% of the initial group. Of these 525 subjects, 114 had used medications related to osteoporosis and were excluded from the study; data were collected from the remaining 411 subjects. The mean age was 48.18 years (Table 1), which was much younger than that of other studies, which have primarily included patients over 70 years of age who exhibited osteoporosis or existing fractures.^{2–4,11} The subjects' mean height, weight, and BMI were 157.92 cm, 53.94 kg, and 21.62 kg/m², respectively (Table 1). Subjects had no history of fragile fracture or history of bone metabolism-related diseases such as diabetes mellitus, collagen disease, liver and/or renal dysfunction, or steroid treatment. Among the 411 subjects, 196 drank in moderation and 41 smoked daily. Fifty-one

Fig. 1 Low 25(OH)D status was more common in younger than in older subjects.

Serum 25(OH)D levels were measured by enzyme-linked immunosorbent assay (ELISA), and the subjects were subdivided into three populations: vitamin D deficiency (< 20 ng/ml), suboptimal (20–30 ng/ml), and normal (> 30 ng/ml).

subjects participated in some sporting activity and spent more than 1 h/week engaged in those activities. Serum levels of calcium (Ca), creatinine (Cr), and tartrate resistant acid phosphatase 5b (TRACP5b) are shown in **Table 1**. The mean serum levels of 25(OH)D and intact PTH were 24.63 (10–55) ng/ml and 52.55 (21–129) pg/ml, respectively (**Table 1**).

Unexpectedly, low serum vitamin D levels were more common in younger than in older subjects, and serum 25(OH)D levels significantly increased with age ($P = 0.019$) (**Figs. 1, 2**).

Increased intact PTH levels in subjects with low 25(OH)D levels

Serum PTH levels are reportedly inversely correlated with serum vitamin D levels.⁸ Indeed, our study demonstrated that serum intact PTH levels were significantly inversely correlated with serum 25(OH)D levels ($P < 0.001$, **Fig. 3A**), i.e., lower 25(OH)D levels were associated with

Fig. 2 Serum 25(OH)D levels increased with age.

Serum 25(OH)D levels were measured by ELISA. A significant correlation was found between serum 25(OH)D levels and age ($P = 0.019$).

higher intact PTH levels. The inverse correlation between 25(OH)D and intact PTH levels in our subjects was further confirmed when PTH levels were found to be significantly higher in subjects with vitamin D insufficiency (below 20 ng/ml) than in those without (greater than 20 ng/ml) (**Fig. 4**).

Levels of 25(OH)D of at least 15–20 ng/ml are reportedly required to achieve optimum PTH levels.^{12,13} In our study, 25(OH)D levels lower than 20 ng/ml were detected in 110 subjects (26.8%), and 18 subjects (4.38%) had serum 25(OH)D levels lower than 15 ng/ml. In the United States, serum 25(OH)D levels lower than 12 ng/ml were reported in 50% of women with osteoporotic hip fractures.⁵ In our study, 6 of 411 subjects (1.46%) had 25(OH)D serum levels lower than 12 ng/ml. However, these six subjects had no history of disease or use of medication that alters bone metabolism.

Changes in 25(OH)D and intact PTH status with age

Serum 25(OH)D and intact PTH levels were inversely correlated ($P < 0.001$), suggesting that younger subjects have lower 25(OH)D levels with higher intact PTH levels than do older subjects. Subjects were subdivided into premenopausal (age 43.6 ± 3.0) and postmenopausal (age 55.2 ± 4.1) populations and analyzed for the relationship between serum PTH and 25(OH)D levels (**Fig. 3B, C**). We found that the younger population showed a more significant inverse correlation between 25(OH)D and PTH levels than did the older population (**Fig. 3A–C**, total population: $r = -0.204$, $P < 0.001$; younger population: $r = -0.219$, $P < 0.001$; older population: $r = -0.183$, $P = 0.02$). Thus, the younger population had lower 25(OH)D and higher intact PTH levels more commonly than did the older population.

Fig. 3 Serum 25(OH)D and Intact PTH levels were inversely correlated.

Serum 25(OH)D and Intact PTH levels were measured by ELISA in all subjects (A), in premenopausal women (B), and in postmenopausal women (C).

Fig. 4 Vitamin D insufficiency is correlated with higher serum Intact PTH levels.

Subjects were subdivided into those with (below 20 ng/ml) and without (greater than 20 ng/ml) vitamin D insufficiency, and serum Intact PTH levels were compared.

Intact PTH status in subjects with or without vitamin D insufficiency

BMI is known to influence 25(OH)D levels.¹⁴ However, in our study, single regression analysis demonstrated that 25(OH)D levels were not influenced by BMI (Table 2, $P = 0.215$). Mild renal dysfunction is known to affect PTH levels.¹⁵ However, we found that Cr, as an indicator of renal function, and PTH levels were not significantly correlated ($P = 0.842$). Some parameters such as age, BMI, and renal function likely affect the relationship between 25(OH)D and intact PTH status.¹⁶ Therefore, we undertook simple regression analysis to examine the relationship between 25(OH)D levels and these parameters.

We found that serum 25(OH)D levels were positively correlated with age and Cr (Table 2).

Next, we performed multiple regression analysis to examine the influence of age, BMI, and Cr on the relationship between 25(OH)D and intact PTH levels (Table 3). We found that intact PTH levels remained significantly and inversely related to 25(OH)D levels, even when adjusted for age, BMI, and Cr (Table 3).

Discussion

Low vitamin D levels have been reported in the general elderly population.^{6,7} Previously, an inverse correlation of 25(OH)D with PTH was reported in elderly women (20 or more years after menopause) but not in younger healthy women (less than 20 years after menopause or premenopause).⁸ However, the present study indicated that younger women had lower serum 25(OH)D levels than did elderly women. The reasons for the relatively lower levels in younger populations reported here compared to older populations are not clear. We consider that the observations reported here may be representative of the general population, because bone density has been shown to be inversely and positively correlated with serum PTH and 25(OH)D, respectively, in healthy women aged 45–65 years, although no age dependency has been shown.¹⁷ Nonetheless, because lower 25(OH)D levels increase the risk of hip and vertebral fractures in the elderly population, our analysis suggests that vitamin D insufficiency in younger individuals should be corrected to prevent future osteoporosis and fractures.^{2–4} Vitamin D sufficiency is reportedly associated with a low incidence of limb and vertebral fractures,¹¹ suggesting that vitamin D supplementation in younger women could reduce fracture risk in the future. It has also been reported that serum vitamin D levels are significantly low, and intact PTH levels are significantly high, in hip fracture patients compared to controls,^{1–3} suggesting that this condition is a risk factor for hip fracture. In Japan, 62% of hip fracture patients

Table 2 Simple regression analysis between 25(OH)D levels and other variables

Variable	β	<i>P</i>
Age	0.116	0.019
BMI	−0.061	0.215
Cr	0.167	0.001

Table 3 Multiple regression analysis between 25(OH)D levels and other variables

		25(OH)D	
		β	<i>P</i>
Adjusted for Age, BMI, and Cr	PTH	−0.185	< 0.001

reportedly have 25(OH)D levels lower than 20 ng/ml.³ In contrast, the same study showed that 18.9% of non-hip fracture controls exhibit vitamin D insufficiency,³ suggesting that this condition is a risk factor for hip fracture.

It is known that sun exposure¹⁴ and dietary vitamin D intake contribute to serum vitamin D status.^{18–20} Ingestion of vitamin D from food or supplements reportedly elevates serum 25(OH)D levels in winter but not in summer,^{18–20} suggesting that vitamin D intake and sun exposure are critical determinants of serum vitamin D levels. In populations living in the northern hemisphere, 25(OH)D levels are reportedly highest in August to October^{21,22}; however, our younger subjects exhibited low 25(OH)D status even in September. Further study is needed to examine the relationship between sun exposure, vitamin D intake, and serum 25(OH)D levels in our subjects. Because younger women often have children in their care, their children may also show low serum vitamin D status, since the children's diet may be similar to that of their parents. We have no data on the vitamin D status of the children of the subjects tested, but we speculate that vitamin D supplementation is also likely recommended for children. Meanwhile, South Asian women living in the UK reportedly have lower 25(OH)D levels than do Caucasian women, and the suggested cause is lower sun exposure in Asians than in Caucasians, rather than dietary reasons.²³ Although 25(OH)D levels are reportedly inversely correlated with BMI in Caucasians,²⁰ we did not observe this relationship in our study. Further study is needed to determine the reasons underlying the lower serum vitamin D status found in our subjects.

Serum 25(OH)D levels greater than 15–20 ng/ml are reportedly required to achieve optimal PTH levels.^{12,13} Chapuy et al. showed a significant inverse correlation between serum 25(OH)D and serum intact PTH levels.²⁴ In our study, 26.8% of subjects had low serum 25(OH)D levels (< 20 ng/ml), and serum PTH levels were significantly and inversely correlated with serum 25(OH)D levels. Lower vitamin D levels result in increased PTH levels, and continuously high PTH levels are known to in-

duce osteoclastogenesis and subsequent bone loss.⁸ This is a likely explanation of why low vitamin D status is a risk factor for hip and vertebral fractures. Therefore, correction of low vitamin D status at a younger age may be important to prevent future osteoporosis.

One limitation of the current study was that all subjects lived in urban areas; therefore, there was little variety in their environmental circumstances. Nonetheless, our study suggests that attention should be paid to vitamin D and intact PTH status in younger populations as well as in the elderly and those suffering fractures.

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Conflict of Interest

All authors have no conflicts of interest to declare.

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