Vitamin D and Prevention of Osteoporosis: Japanese Perspective*

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Abstract

Vitamin D insufficiency, or a low vitamin D status, is a prevalent condition worldwide. However, there have been no studies addressing this public health issue until recently. In this review article, a summary of a series of studies conducted by the author and his colleagues to determine whether the vitamin D status of Japanese people is adequate and how their vitamin D status affects bone mass and bone metabolism is presented. The observational studies conducted by our group revealed that vitamin D insufficiency does not seem to be a serious problem among active elderly people, but that elderly people with a low level of activities of daily living (ADL) are at a very high risk of vitamin D insufficiency. In young adults, a high intact PTH concentration due to vitamin D insufficiency, which adversely affects their bone mass, is common, suggesting that vitamin D nutrition, as well as dietary calcium intake, should be improved. However, the effects of vitamin D insufficiency among elderly Japanese on bone metabolism, bone mass, and fractures have not been clarified, and should be studied further to determine whether specific preventive strategies, such as vitamin D supplementation, are required for this high-risk group. Intervention studies targeting Japanese populations are required to further address this issue.

Key words: 25-hydroxyvitamin D, Japanese, osteoporosis, prevention, vitamin D

Introduction

Osteoporosis is an age-related disease characterized by generalized skeletal fragility in which bone strength becomes so weak that fractures can occur from minimal trauma (1). Fractures due to osteoporosis are becoming increasingly more common in Japan. One epidemiologic study indicates that the incidence of femoral neck fractures in Japan has more than doubled over the last two decades (2). Osteoporotic fractures, particularly spine and hip fractures, decrease the level of activities of daily living (ADL) and the quality of life among the elderly, and significantly increase medical costs. Although osteoporosis has mainly been treated with therapeutic medicine, it is also important to address the role of preventive medicine.

A low vitamin D status is a prevalent condition worldwide and is believed to be a preventable risk factor for osteoporosis.

Table 1 shows the major risk factors for osteoporosis. In 1995, the European SENECA Study group published results indicating that latitude positively correlates with vitamin D status in the elderly, such that the mean serum 25-hydroxyvitamin D (an index of vitamin D status) concentration was the highest (48 nmol/L) in Norway (61° north) and the lowest (21 nmol/L) in Greece (35° north) among women (3). This observation was partly explained by the idea that people living in low latitudes, as compared with those living in high latitudes, do not engage in lifestyles that promote vitamin D nutrition, such as taking a sunbath in the winter and taking vitamin D supplements. This

Table 1 Major risk factors for osteoporosis

Intrinsic causes
Female gender
Ageing
Menopause or low estrogen level
Ethnicity (Caucasians)
Heredity
Extrinsic causes
Decreased weight-bearing physical activity
Inadequate nutrition conditions (e.g. low calcium intake, vitamin D insufficiency, and leanness)
Smoking and alcohol drinking
Secondary causes
Corticosteroid treatment, bilateral oophorectomy, and others

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study suggested that even people living in low latitudes may have an inadequate vitamin D status, which prompted this review article as the first step towards creating a strategy for preventing osteoporosis. In this review article, a summary of a series of studies conducted by the author and his colleagues to determine the relationship between vitamin D nutritional status and bone health in Japan, and to determine whether the vitamin D status of Japanese people is adequate and how their vitamin D status affects bone mass and bone metabolism is presented.

Vitamin D metabolism in humans

Vitamin D is obtained by the human body from food and the skin's exposure to ultraviolet B radiation. Therefore, vitamin D is regarded as a nutrient, as well as a hormone. Figure 1 illustrates the pathways of vitamin D metabolism. Once vitamin D moves into the blood stream, it is promptly converted into 25(OH)D by 25-hydroxylase in the liver. 25(OH)D is relatively stable in the human body and is therefore a good indicator of vitamin D nutritional status. 25(OH)D is ultimately converted into 1,25-dihydroxyvitamin D (1,25(OH)₂D), the most active form of vitamin D, in the kidney. 1,25(OH)₂D has various physiological functions in maintaining normal bone metabolism in the human body; its target organs include the bone, intestine, and parathyroid gland (4). Although 25(OH)D has long been known as a nonactive form of vitamin D, recent studies show that it also has certain biological effects, including the acceleration of calcium absorption in the intestine (5).

Vitamin D insufficiency

Vitamin D plays an important role in maintaining normal bone metabolism, as evidenced by the fact that vitamin D deficiency causes rickets and osteomalacia. Although rickets are no longer commonly found, a moderate decrease in vitamin D level, such as in vitamin D insufficiency, is increasingly becoming a concern. Figure 2 illustrates the spectrum of the vitamin D nutritional status. Vitamin D deficiency is characterized by a very low serum 25(OH)D concentrations <12.5 nmol/L (5 ng/mL) that can cause severe secondary hyperparathyroidism, high bone turnover, and impaired mineralization in the bone (6). Conversely, the serum 25(OH)D concentration in vitamin D insufficiency is low, but not as low as that in vitamin D deficiency, and does not inhibit mineralization. Vitamin D insufficiency is associated with a slightly abnormal bone metabolism, such as mild hyperparathyroidism, and is therefore recognized as a risk factor for a low bone mass and osteoporosis among the elderly. The cutoff serum 25(OH)D concentration used to diagnose vitamin D insufficiency remains controversial. Previously reported values ranged widely from 30 nmol/L (12.5 ng/mL) to 110 nmol/L (44 ng/mL) (7, 8), mainly owing to variabilities in the types of population targeted, determination of serum 25(OH)D concentration, and the use of various outcome measures. The outcome measures used to indicate an inadequate vitamin D status include blood parathyroid hormone (PTH) concentration, calcium absorption level in the intestine, bone mineral density (BMD), and fracture occurrence. Among these measures, blood PTH concentration is often used to diag-

Fig. 1 Vitamin D is converted into 25(OH)D by 25-hydroxylase, a good indicator of vitamin D nutritional status, in the liver. 25(OH)D is ultimately converted into 1,25-dihydroxyvitamin D (1,25(OH)₂D), the most active form of vitamin D, in the kidney.

Fig. 2 Spectrum of vitamin D nutritional status and its effects on parathyroid function and bone. The cutoff point between vitamin D insufficiency and sufficiency is estimated to be 50 nmol/L (20 ng/mL), but is yet uncertain in Japanese adults.

nose vitamin D insufficiency, on the basis of a cutoff serum 25(OH)D concentration, below which serum intact PTH concentration begins to increase. The conservative serum 25(OH)D concentration range used to diagnose vitamin D insufficiency is 25–37.5 nmol/L (10–15 ng/mL). However, values higher than this range, such as 50 nmol/L (20 ng/mL), 75 nmol/L, and 80 nmol/L, have recently been suggested (8–10). For these reasons, comparing the prevalence of vitamin D insufficiency between populations is difficult.

Vitamin D insufficiency in Europe and North America

Numerous studies have reported the prevalence of vitamin D insufficiency in European and North American countries located in high latitudes, where low vitamin D status has been a major health problem, particularly during the winter. Large-scale epidemiologic studies conducted in these countries are summarized herein. Chapuy et al. (11) reported vitamin D insufficiency (cutoff serum 25(OH)D concentration of 30 nmol/L) in 14% of ambulant elderly people in France in a nationwide epidemiologic study conducted over a calendar year. Lips et al. (12) conducted an international multicenter study and reported

that the prevalence of vitamin D insufficiency (cutoff serum 25[OH]D concentration of 25 nmol/L) is approximately 10% in middle-aged and elderly people living in middle and southern Europe, but only 5% or lower among people living in northern Europe and North America. These studies suggest that vitamin D insufficiency is a global health problem that occurs not only in high-latitude countries, but also in low-latitude countries. The prevalence of vitamin D insufficiency appears to be much higher among the frail elderly. Gloth et al. (13) reported that approximately half of the home-bound elderly in the United States suffer from vitamin D insufficient (cutoff serum 25[OH]D concentration of 25 nmol/L).

Serum 25(OH)D concentration and vitamin D insufficiency in Japanese elderly populations

The author and his colleagues studied serum 25(OH)D concentration, and the prevalence of vitamin D insufficiency and intact PTH concentration in various Japanese populations. Table 2 shows that the mean serum 25(OH)D concentration varies with season and activity level. The mean serum 25(OH)D concentrations in the healthy elderly living in communities were relatively high (59.9–78.8 nmol/L) (14–16) and comparable to the highest mean serum 25(OH)D concentration reported by Jacques et al. (17). When the cutoff serum 25(OH)D concentration was defined as 30 nmol/L (12 ng/mL), the prevalence of vitamin D insufficiency in the healthy elderly living in communities was estimated to be less than 5% (8, 14–16). This value suggests that vitamin D insufficiency in ambulant elderly Japanese is not a major problem. In contrast, the mean serum 25(OH)D concentration and the prevalence of vitamin D insufficiency among the elderly with a low ADL level (elderly requiring home care and frail nursing home residents) (18, 19) were respectively lower and higher than those among the ambulant elderly. Figure 3 shows that there is a positive correlation between ADL level and serum 25(OH)D concentration in the elderly who require care (17). Furthermore, about half of the nursing home residents in this study showed vitamin D insufficiency (18). The low serum 25(OH)D concentration in the frail elderly is mainly due to limited exposure to sunlight

and the decreased biosynthesis of vitamin D in the skin. A low ADL level appears to be the most important risk factor for vitamin D insufficiency in elderly Japanese.

Another major determinant of serum 25(OH)D concentration among the Japanese is the intake of fish (20, 21), some of which contains a considerable amount of vitamin D (22). The author and his colleagues confirmed that elderly people who ate fish at least 4 days per week during the winter had a serum 25(OH)D concentration that was approximately 10 nmol/L higher than that of those who did not (15). Similar findings were also found in the elderly requiring care, regardless of the season (17). These findings indicate that frequent fish intake is important in improving the vitamin D status in the Japanese population. However, fish is not an important source of vitamin D in most Europeans and North Americans.

Fig. 3 Scatter plots of serum 25-hydroxyvitamin D (25[OH]D) concentration against total Barthel index score. Log-transformed serum 25(OH)D concentrations showed linear regressions with the Barthel index scores in winter (solid line, $R^2=0.099$, $P=0.0001$) and in summer (dotted line, $R^2=0.125$, $P<0.0001$). Reproduced from reference (17) with permission.

Table 2 Mean serum 25-hydroxyvitamin D (25[OH]D) concentrations and prevalences of vitamin D insufficiency (<30 nmol/L or 12 ng/ml) and high intact PTH concentrations (>6.9 nmol/L or 65 pg/ml) in middle-aged and elderly Japanese populations

Ref.	Subjects	Time period	Serum 25(OH)D* concentration (nmol/L)	Prevalence of vitamin D insufficiency (%)	Prevalence of high serum intact PTH concentration (%)
(14, 15)	160 ambulant women living in community (mean age, 65.6)	September	78.8	0	0
		February	59.9	4.6	2.0
(16)	144 ambulant women living in community (mean age, 66.5)	June	65.1	2.7	—
(8)	582 ambulant women living in community (mean age, 74.5)	May–June	59.9	3.3	4.8
(17)	143 people requiring care at home (mean age, 82.9)	February, March	54.2	15.4	8.4
		August–September	53.3	20.8	8.3
(18)	133 frail nursing home residents (mean age, 84.6)	October–December	29.9	57.9	15.8

* Serum 25(OH)D concentrations were determined either by high-performance liquid chromatography (14–16, 19) or chemiluminescent assay (8, 18).

Vitamin D insufficiency in young

An important strategy for preventing osteoporosis is to attain a maximal peak bone mass, particularly for women during their youth. Yet, very little attention has been given to determine whether vitamin D status is adequate in young people. Furthermore, until recently, few studies have been conducted concerning vitamin D insufficiency in this population. The author and his colleagues investigated the vitamin D status in young adults and reported that the serum 25(OH)D concentration in women in their 20s was significantly lower than those in middle-aged and elderly women (23, 24). This may, in part, be due to a lower vitamin D intake among younger women (25). Another study on healthy young women showed the prevalence of low serum 25(OH)D concentrations (<30 nmol/L or 12 ng/mL) in 30% and high intact PTH concentrations (>6.9 pmol/L or 65 pg/mL) in 16% of the women (26). A negative association, which is typically seen in the elderly, was found between the serum 25(OH)D and intact PTH concentrations in this study (26). Figure 4 shows that the high intact PTH group had lower BMDs in both the spine and hip than the normal intact PTH group (26). It was surprising to discover that healthy young women had mild, secondary hyperparathyroidism (due to vitamin D insufficiency), which adversely affected their bone mass and bone metabolism. Collectively, these findings indicate that vitamin D insufficiency is prevalent not only in the elderly, but also in the young, and may be an obstacle for attaining a maximal peak bone mass.

Effects of vitamin D on bone mass and fractures

A number of observational and intervention studies conducted in European and North American countries have shown that serum 25(OH)D concentration is associated with BMD and that vitamin D supplementation prevents age-related bone loss and fractures in the elderly (27). In addition, a low vitamin D status has been shown to be associated with decreased muscle strength and body balance and an increase in the occurrence of falls (28). A recent review by Bischoff-Ferrari et al. (10) suggested that the optimal serum 25(OH)D concentration is 75 nmol/L or higher, when multiple outcomes, such as age-related bone loss, fractures, lower-extremity function and falls, are considered. A vitamin D (cholecalciferol) intake of at least 800 IU/day (32 µg/day) is recommended for Caucasians (10, 29) in order to attain a serum 25(OH)D concentration of 75 nmol/L. This level represents 2- to 3-fold the vitamin D intake of elderly Japanese. Detailed information about the efficacy of vitamin D on osteoporosis has been published elsewhere (27).

Vitamin D for the prevention of osteoporosis in Japan

The average intake level of dietary vitamin D among elderly Japanese is estimated to be in the range of 300–400 IU/day (12–16 µg/day) (20, 21, 25). From the current data (800 IU/day vitamin D supplement recommended) (10, 29) derived mainly from Caucasian populations, an additional intake level

Fig. 4 Young women (mean age, 21) with high intact PTH concentrations (>6.9 pmol/L or 65 pg/mL) had significantly lower bone mineral densities (BMDs) in the spine and hip (femoral neck) than women in the normal intact PTH group.

of 400–500 IU/day (16–20 µg/day) vitamin D may be effective in preventing bone loss and osteoporotic fractures. However, such a vitamin D intake level cannot be taken in by normal diet, but can be taken in through the use of supplements.

It may not be appropriate to apply study findings based on data from Caucasian populations to the Japanese population because the occurrence of osteoporosis and calcium intake level (a major nutritional factor related to the bone metabolism) differ between these populations. Furthermore, only a few studies have been conducted in Japan to clarify the relationship between vitamin D status and bone loss or osteoporotic fractures. The author and his colleagues have conducted several cross-sectional studies indicating that serum 25(OH)D concentrations of 40–50 nmol/L (thresholds depending on the ADL levels of populations) or lower are associated with secondary hyperparathyroidism in the elderly (8, 17) and that the serum 25(OH)D concentrations of 40 nmol/L or lower are associated with poor body balance (30). However, these studies did not clarify the association between vitamin D status and bone loss. In addition, neither longitudinal studies nor randomized controlled trials in Japanese populations have been conducted. These studies are highly encouraged for the near future.

Summary

A series of studies conducted by the author and his colleagues indicate that vitamin D insufficiency does not appear to be a serious problem among active elderly people, but that the elderly with low ADL levels are at a very high risk of vitamin D insufficiency. These studies suggest that moderate sunbathing and a fish-rich diet are important in maintaining an adequate vitamin D status for Japanese. Nonetheless, the effects of vitamin D insufficiency on bone metabolism, bone mass, and fractures among the elderly Japanese have yet to be clarified. Future studies should explore whether specific preventive strategies, such as vitamin D supplementation, are required for this high-risk group. Among young adults, a high intact PTH concentration due to vitamin D insufficiency is found and can adversely affect their bone mass, suggesting that vitamin D nutrition, as well as dietary calcium intake, should be improved.

Researchers in European and North American countries have proposed that the optimal serum 25(OH)D concentrations range is 70–80 nmol/L (28–32 ng/mL) or higher on the basis of the results of randomized controlled trials. Conversely, an adequate serum 25(OH)D concentration in Japan has been proposed to be 50 nmol/L (20 ng/mL) or higher, the basis of the results of observational studies. Intervention studies targeting Japanese populations should be conducted to better understand the potential differences in 25(OH)D thresholds.

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