

Assessment criteria for vitamin D deficiency/insufficiency in Japan: proposal by an expert panel supported by the Research Program of Intractable Diseases, Ministry of Health, Labour and Welfare, Japan, the Japanese Society for Bone and Mineral Research and the Japan Endocrine Society [Opinion]

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Abstract Vitamin D is indispensable for the maintenance of bone and mineral health. Inadequate vitamin D action increases the risk for various musculoskeletal/mineral events including fracture, fall, secondary hyperparathyroidism, diminished response to antiresorptives, rickets/osteomalacia, and hypocalcemia. Its most common cause in recent years is vitamin D deficiency/insufficiency, clinically defined by a low serum 25-hydroxyvitamin D [25(OH)D] level. Guidelines for vitamin D insufficiency/deficiency defined by serum 25(OH)D concentrations have been published all over the world. In Japan, however, the information on the associations between serum 25(OH)D and bone and mineral disorders has not been widely shared among healthcare providers, partly because its measurement had not been reimbursed with national medical insurance policy until August 2016. We have set out to collect and analyze

Japanese data on the relationship between serum 25(OH)D concentration and bone and mineral events. Integrating these domestic data and published guidelines worldwide, here, we present the following assessment criteria for vitamin D sufficiency/insufficiency/deficiency using serum 25(OH)D level in Japan. (1) Serum 25(OH)D level equal to or above 30 ng/ml is considered to be vitamin D sufficient. (2) Serum 25(OH)D level less than 30 ng/ml but not less than 20 ng/ml is considered to be vitamin D insufficient. (3) Serum 25(OH)D level less than 20 ng/ml is considered to be vitamin D deficient. We believe that these criteria will be clinically helpful in the assessment of serum 25(OH)D concentrations and further expect that they will form a basis for the future development of guidelines for the management of vitamin D deficiency/insufficiency.

Keywords Vitamin D · Vitamin D deficiency · 25-Hydroxyvitamin D · Fracture · Parathyroid hormone

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Definition and significance

Normal vitamin D action is indispensable for the maintenance of bone and mineral metabolism. Inadequate vitamin D action results in various abnormalities in bone and mineral metabolism, including an increase in fracture risk. The most common cause of diminished vitamin D action at present days is vitamin D insufficiency/deficiency, a decrease in body stores of vitamin D. Vitamin D status can only be assessed with measurement of serum 25-hydroxyvitamin D [25(OH)D]. Guidelines for vitamin D insufficiency/deficiency defined by serum 25(OH)D concentrations have been published from many countries and regions all over the world [1–5]. In Japan, however, the information on the associations between serum 25(OH)D and bone

Table 1 Assessment criteria for vitamin D deficiency/insufficiency in Japan

1. Serum 25(OH)D level equal to or above 30 ng/ml is considered to be vitamin D sufficient
2. Serum 25(OH)D level less than 30 ng/ml is considered to be not vitamin D sufficient
 - (a) Serum 25(OH)D level less than 30 ng/ml but not less than 20 ng/ml is considered to be vitamin D insufficient
 - (b) Serum 25(OH)D level less than 20 ng/ml is considered to be vitamin D deficient

Notes

- 1) Serum 25(OH)D level may vary depending on the assays used. Standardization of the assay will be needed.
- 2) Different criteria may be needed for children and pregnant or lactating women. On nutritional vitamin D deficient rickets in children, there is a published global consensus [6].
- 3) These assessment criteria have been established from the standpoint of bone and mineral metabolism.
- 4) Besides bone and mineral abnormalities, many disorders including cancers, metabolic, cardiovascular and immunological diseases have been linked to low serum 25(OH)D levels. Most such studies have, however, been conducted overseas. And no vitamin D guidelines have dealt with potential vitamin D actions beyond bone and mineral metabolism. Thus, the present assessment criteria will not consider vitamin D actions beyond bone and mineral metabolism.

and mineral disorders has not been widely shared among healthcare providers, partly because serum 25(OH)D measurement had not been reimbursed with national medical insurance policy until August 2016. Thus, we have set out to collect and analyze Japanese data on the relationship between serum 25(OH)D concentration and bone and mineral events such as osteoporotic fractures. Integrating these domestic data and published guidelines worldwide, here, we present the first version of assessment criteria for vitamin D sufficiency/insufficiency/deficiency using serum 25(OH)D level in Japan (Table 1).

In the present assessment criteria, as in the 2011 US Endocrine Society guideline [1], we use the term “vitamin D insufficiency” for relatively mild vitamin D insufficient state, and the term “vitamin D deficiency” for a severe vitamin D-insufficient state. Clinically, both vitamin D insufficiency and deficiency may cause increases in fracture and fall risks, secondary hyperparathyroidism, and poor responses to antiresorptives. Vitamin D deficiency can further cause rickets/osteomalacia and hypocalcemia.

The present assessment criteria are not guidelines for the diagnosis of vitamin D deficiency/insufficiency. Development of clinical guidelines including needs for medical intervention will be a future task.

Explanations**Clinical definition and significance of vitamin D insufficiency/deficiency**

Vitamin D insufficiency/deficiency is a state where body stores of vitamin D decrease, which may result in insufficient vitamin D action. Animals, including humans, can synthesize vitamin D₃ in the skin using ultraviolet energy. Plants contain vitamin D₂. Both vitamin D₃ and D₂ follow the same metabolism, and their actions are qualitatively

the same. Thus, we use the collective term “vitamin D”. Most vitamin D synthesized in the skin or orally ingested is converted to 25(OH)D in the liver. 25(OH)D makes a stable complex with vitamin D binding protein (DBP) in the circulation. Because the half-life of circulating 25(OH)D is relatively long, about 3 weeks, serum 25(OH)D level is considered to reflect the amount of vitamin D stores. Therefore, vitamin D insufficiency/deficiency is clinically defined as a state characterized by low serum 25(OH)D, which may result in insufficient vitamin D action.

Classical action of vitamin D is the maintenance of bone and mineral metabolism. Abnormalities resulting from insufficient classical action of vitamin D are listed in Figure 1. Insufficient action of vitamin D can result in impaired absorption of calcium (Ca) and phosphate (P) from the intestine, thereby causing hypocalcemia and/or hypophosphatemia. Such abnormalities may in turn impair bone mineralization, resulting in rickets/osteomalacia, and may also cause secondary hyperparathyroidism further leading to stimulated bone resorption and decreased bone mineral density. In addition, low serum 25(OH)D level is a risk factor for falling. Altogether, fracture risk increases with low serum 25(OH)D level. The lower the serum 25(OH)D level is, the higher is the risk of those abnormalities. Low serum 25(OH)D level has also been reported to be associated with poor responses to antiresorptive medications (Fig. 1).

Besides 25(OH)D, other vitamin D metabolites such as 1 α ,25-dihydroxyvitamin D or 1,25(OH)₂D, which is 1 α -hydroxylated 25(OH)D in the proximal tubules, are present in circulation. Most vitamin D actions are mediated by the vitamin D receptor (VDR), a member of the nuclear receptor super-family. Among physiological vitamin D metabolites, 1,25(OH)₂D has the highest affinity to VDR. Until recently, physiological production of 1,25(OH)₂D had been considered to be restricted to the proximal tubule. However, recent studies have revealed that 1 α -hydroxylase is present in vitamin D

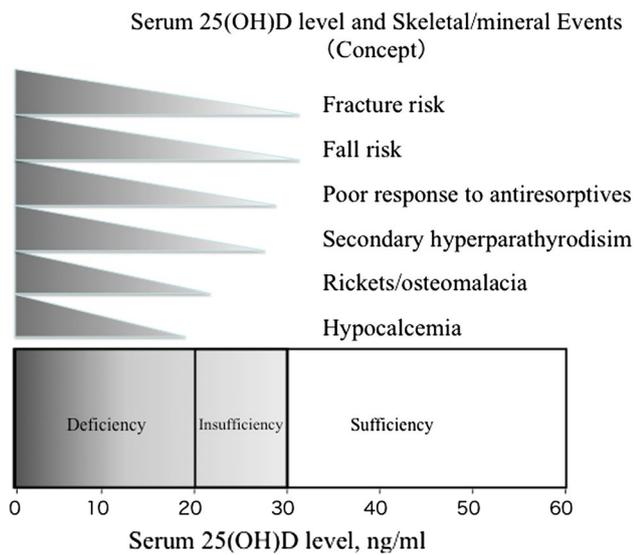


Fig. 1 Serum 25(OH)D level and skeletal/mineral events (concept). The lower the serum 25(OH)D level is, the higher the risk is for the musculoskeletal/mineral events. Note that each event has a unique threshold 25(OH)D level

target organs such as bone [7, 8] and parathyroid [9, 10], and that cells in those tissues can produce $1,25(\text{OH})_2\text{D}$. Therefore, vitamin D actions in these target organs are not only brought by circulating $1,25(\text{OH})_2\text{D}$ produced in the kidney, but most likely exerted also by $1,25(\text{OH})_2\text{D}$ locally produced from 25(OH)D taken up from the circulation into the cell, the concentration of which is approximately 1000 times higher than that of $1,25(\text{OH})_2\text{D}$ in the blood.

In vitamin D deficiency/insufficiency, associated hypophosphatemia and secondary hyperparathyroidism may stimulate 1α -hydroxylase in the proximal tubule, frequently resulting in high serum $1,25(\text{OH})_2\text{D}$ levels. Indeed, serum $1,25(\text{OH})_2\text{D}$ levels in vitamin D deficiency/insufficiency cases have been reported to be normal, high, or low. In addition, the half-life of circulating $1,25(\text{OH})_2\text{D}$ is less than a day. Thus, serum $1,25(\text{OH})_2\text{D}$ level reflects neither tissue vitamin D actions, nor the vitamin D status.

Relationship between serum 25(OH)D level and bone/mineral events in the Japanese

Fracture

Several Japanese observational studies have reported associations between low serum 25(OH)D levels and osteoporotic fractures, including hip fractures. One study reported that the mean serum 25(OH)D level of 50 patients admitted for hip fracture was 17.8 ng/ml, which was significantly lower than that of 53 non-hip fracture control patients (25.8 ng/ml) [11]. Another study reported that the mean serum 25(OH)D level

of 225 patients who visited an hospital for hip fracture was 16.3 ng/ml, significantly lower than 18.1 ng/ml, the mean serum 25(OH)D level of 63 patients who had new clinical vertebral fracture during the same period [12]. Others [13] reported that among 330 untreated postmenopausal Japanese women who visited an orthopedic clinic, prevalent vertebral fractures were more frequent in those with a serum 25(OH)D level less than 20 ng/ml than in those with 20 ng/ml or more. There is also a report [14] demonstrating that among 202 postmenopausal Japanese women, the mean serum 25(OH)D level in those with prevalent fractures was 14.6 ng/ml, which was significantly lower than that in those without. The Muramatsu study [15], a 6-year cohort study of 773 community-dwelling women in Niigata prefecture, revealed that fracture risk was significantly lower in subjects with basal serum 25(OH)D level being more than 28.4 ng/ml compared with the others with lower 25(OH)D levels, with the hazard ratio of 0.41 (95% CI 0.18–0.91). Another cohort study of 1470 postmenopausal women conducted in Nagano prefecture with a mean observation period of 7.2 years [16] revealed that those with a basal serum 25(OH)D level less than 25 ng/ml showed a significantly higher risk of long-bone fracture. Finally, the Japanese Population-based Osteoporosis (JPOS) study [17] reported that among 1262 postmenopausal women, 5-year total fracture incidence was highest in the group with basal serum 25(OH)D level less than 10 ng/ml, followed by those with between 10 and 20 ng/ml, and the lowest in the group above 30 ng/ml.

Bone mineral density (BMD)

The Yokogoshi study [18] conducted in Niigata prefecture reported that serum 25(OH)D level was positively associated with femoral neck BMD, which was more frequently in the osteoporotic range in subjects with serum 25(OH)D levels less than 20 ng/ml compared with control subjects with levels above 28 ng/ml. At least one other Japanese study reported positive correlation between BMD and serum 25(OH)D level [14]. A recent study of 1380 Japanese male and female teenagers between 12 and 18 years old reported positive correlations between serum 25(OH)D and calcaneal stiffness, which was significantly lower in those with serum 25(OH)D less than 20 ng/ml [19].

Parathyroid hormone (PTH)

Several cross-sectional studies reported negative correlation between serum PTH and serum 25(OH)D levels in the Japanese [17, 20], which may be explained by locally produced $1,25(\text{OH})_2\text{D}$ in the parathyroid glands. A Japanese study investigating PTH responsiveness to vitamin D_3 loading estimated that a serum 25(OH)D level of 28 ng/ml would be the minimal threshold to prevent PTH

hypersecretion [20]. Among cross-sectional studies, in the aforementioned Yokogoshi study [18], serum PTH level was significantly higher in subjects with serum 25(OH)D level being less than 20 ng/ml. The Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study [21] reported that PTH level was highest in the group with serum 25(OH)D less than 10 ng/ml, followed by the group with 10–30 ng/ml, and lowest in those above 30 ng/ml, and that the difference among the three groups was significant.

Fall

A study of the community-dwelling elderly reported that a serum 25(OH)D level less than 20 ng/ml was associated with a higher fall incidence in the previous year among women aged 65 years or more [22]. Follow-up study revealed that a serum 25(OH)D level less than 20 ng/ml was also associated with a higher fall incidence in the following year among women over 75 years old [23].

Responsiveness to antiresorptive medications

Ishijima et al. reported that a serum 25(OH)D level less than 25 ng/ml was associated with significantly weaker BMD response to alendronate [24]. Reports from other countries indicated serum 25(OH)D levels less than 30–32 ng/ml were associated with poorer BMD responses to bisphosphonates and selective estrogen receptor modulators or with increased fracture incidence during anti-osteoporotic pharmaceutical treatment [25–28].

Osteomalacia and rickets

According to the “Pathogenesis and diagnostic criteria for rickets and osteomalacia—proposal by an expert panel supported by the Ministry of Health, Labour and Welfare, Japan, the Japanese Society for Bone and Mineral Research, and the Japan Endocrine Society” [29], serum 25(OH)D levels less than 20 ng/ml may cause vitamin D deficient rickets/osteomalacia. “Global Consensus Recommendations on Prevention and Management of Nutritional Rickets” [6] indicated that serum 25(OH)D levels less than 12 or 20 ng/ml combined with Ca intake deficiency increase the risk of nutritional rickets in children. On the other hand, a German study of 665 adult autopsies reported that a serum 25(OH)D level up to 30 ng/ml was associated with a histological mineralization defect [30].

Hypocalcemia

“The Guide for the Differential Diagnosis of Hypocalcemia” compiled by the Japan Endocrine Society [31] indicated that a serum 25(OH)D level less than 15 ng/ml is

highly suggestive of the diagnosis of hypocalcemia due to vitamin D deficiency.

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Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest.

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