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# High Frequency of Vitamin D Deficiency in Patients with Rheumatoid Arthritis

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**Abstract**

**Objectives:** Vitamin D (VD) has multiple physiological function including bone-mineral metabolism and musculo-skeletal effects. The purpose of this study is to disclose actual circumstances of VD contentment and characteristics in patients with Rheumatoid Arthritis (RA).

**Methods:** Serum VD levels of 132 outpatients with RA consecutively selected in our hospital were estimated. The relationship between serum VD levels and various clinical indices was investigated.

**Results:** Mean serum concentration of 25-hydroxyvitamin $D_3$ (25OHD) in total subjects was 18.1ng/ml, which was regarded as apparent VD deficiency. Importantly, 60% of the subjects showed less than 20ng/ml, and only 5% exceeded 30ng/ml which fulfilled sufficient VD level. In contrast, mean serum 1α, 25-dihydroxyvitamin $D_3$ level was 37.9 pg/ml, which was within the normal reference value. Disease activity and various serum chemistry data were not related to the VD levels. Instead, there was a tendency that higher Steinbrocker's functional class was associated with lower serum 25OHD level.

**Conclusion:** From these results, we concluded that frequency of VD deficiency in RA patients is high and it is supposed that low physical activity is closely related to VD deficiency. Appropriate VD supplementation should be considered a part of comprehensive management of RA patients.

**Keywords:** Rheumatoid arthritis; Vitamin D deficiency; 25-hydroxyvitamin D.

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## Introduction

Rheumatoid Arthritis (RA) is a systemic autoimmune inflammation of which pathogenesis involves a complex interplay among genotype, environmental triggers, and chance [1]. RA is typically characterized by persistent synovitis, which leads to invasion of macrophage-like synoviocytes into cartilage and finally joint destruction [2], thereby affecting patients' normal musculo-skeletal function. Systemic inflammation [3], decreased physical activity [4] and concomitant use of glucocoritoids [5] also promotes generalized bone loss, leading to exacerbation of osteoporosis and high frequency of fracture in RA patients [6].

Vitamin D (VD) is essential for the development and maintenance of bone health from birth until death [7]. Although VD is taken orally as well, majority of VD store is derived from solar ultraviolet (UV) B exposure which stimulates conversion of 7-dehydrocholesterol to VD in the skin [8]. VD, both from dietary and UV-induced, is metabolized in the liver to 25-hydroxyvitamin $D_3$ (25OHD), then finally metabolized in the kidney to 1, 25-dihydroxyvitamin $D_3$ [1,25$(OH)_2$D], a biologically active form. Generally, circulating 25OHD level reflects patients' VD status [9].

1, 25$(OH)_2$D is a lipid-soluble hormone that interacts with VD Receptors (VDRs) expressed in various tissues or cells, and exerts pleiotropic effects. Not only Bone Mineral Density but also variety of physiological function has been disclosed. Low serum 25OHD level is significantly associated with low bone mineral density (BMD) [10] and increased risk of nonvertebral and hip fracture [11,12]. Optimal VD concentration is associated with maintenance of lower-extremity strength [13], and reported to reduce the risk of falling [14]. In addition, VD inhibits production of proinflammatory cytokines such as IL-6 and TNFα from human monocytes *in-vitro* [15]. All of these findings strongly suggest the beneficial effects of VD on RA patients, and RA patients should satisfy the optimal serum concentration of VD.

Although several reports [16-20] which showed serum VD levels and clinical relevance in RA patients appeared previously, these studies were performed in the subjects with ethnic difference and different lifestyles from Japanese patients. In the present study, we demonstrate actual circumstances of serum VD levels in Japanese RA patients in our clinical setting.

## Subjects and Methods

### Subjects

Blood samples were taken from 132 Japanese RA patients, who visited Kyushu University Beppu Hospital, Beppu, Japan (latitude 33.2 degrees North) during June 2011 for routine check-up. This study was approved by the ethical committee of Kyushu University Hospital. Patients who were given an informed consent were enrolled in the study. All patients fulfilled the 1987 American College of Rheumatology criteria for RA [21].

### Blood sampling and Vitamin D assay

After fasting blood samples were taken, serum was immediately separated by centrifugation and stored at -80 ˚C until analysis. Samples were consigned to a commercial clinical laboratory (SRL, Tokyo, Japan) for VD assay. Serum 25OHD and 1, 25$(OH)_2$D were measured collectively using specific radioimmunoassay kits (25-Hydroxyvitamin D $^{125}$I RIA Kit, DiaSorin, Inc., Stillwater, MN, USA; 1,25$(OH)_2$D RIA Kit, Immnodiagnostic Systems, Tyne and Wear, UK). The intra- and inter-assay coefficients of variation were 5.96 % to 6.99 % and 4.36 % to 6.29 %, respectively.

Serum levels of CRP, AST, ALT, alkaline phosphatase, blood urea nitrogen, creatinine, calcium, phosphorus and albumin were measured using the same samples. The estimated Glomerular Filtration Rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [22].

### Profiles of the subjects

Following information about subjects was collected from the medical records; age, gender, complications, disease-related variables including onset and duration of the disease, Steinbrocker radiographic stage and functional class [23], concomitant use of corticosteroids, methotrexate (MTX) or biologics, 28 Tender Joint Count (TJC28), 28 Swollen Joint Count (SJC28), serum levels of CRP. The three-variable Disease Activity Score (DAS28) was calculated using C-Reactive Protein (CRP) and the Nijmegen formula [24]. Concurrent prescription of drugs affecting bone metabolism including bisphosphonates, calcium and VD was also investigated. Subjects were also interviewed about voluntary use of vitamins, health foods and supplements. Although we found high frequency of health food users in RA patients [25], all patients negated use of such agents within one month before this survey.

## Statistical Methods

For statistical analysis, association of serum 25OHD levels and disease status was determined by using analysis of variance (ANOVA), Chi-square test and Kruskal-Wallis test. All analyses were performed with the use of statistical software JMP 9.0 (SAS, Cary, NC, USA). P values smaller than 0.05 were considered significant.

## Results

Demographical characteristics and the clinical parameters of the subjects enrolled in the survey are summarized in table 1. The total 132 subjects comprised 107 females and 25 males. The median Inter Quartile Range (IQR) age was 63 (29 - 87) years old, having median disease duration of 10.0 years (0 - 58). Subjects classified with Steinbrocker's radiographic stages I to IV formed 25.0 %, 23.4 %, 22.6 % and 29.0 %, respectively. And those classified with Steinbrocker's functional classes 1 to 4 formed 21.2 %, 65.2 %, 10.6 % and 3.0 %, respectively. Prednisolone, with a median daily dose of 5.0 mg (0 - 10), was prescribed to 74.2% of the patients. Methotrexate was prescribed to 55.3 % of the patients, with a median daily dose of 6.0 mg (0 - 12). 1α (OH)vitamin $D_3$ was prescribed to 22 patients (16.7%). Bisphosphonate was prescribed to 52 patients (39.4%). The majority of the patients had stable disease condition with median DAS28-CRP score of 2.18 (1.15 - 6.58) (Table 2).

**Table 1:** Characteristics of the patients at the point of serum vitamin D evaluation

| | 132<br>25/107 |
|---|---|
| Age | Median 63 yrs (29-87 yrs) |
| Disease duration | Median 10 yrs (1-58 yrs) |
| Steinbrocker's radiographic stage | |
| I | 25.0% |
| II | 23.4% |
| III | 22.6% |
| IV | 29.0% |
| Steinbrocker's functional class | |
| 1 | 21.2% |
| 2 | 65.2% |
| 3 | 10.6% |
| 4 | 3.0% |
| Concomitant medication | |
| Prednisolone | 74.2% |
| Methotrexate | 55.3% |
| 1α (OH) $D_3$ | 16.7% |
| Bisphosphonate | 39.4% |
| Serum 25OHD concentration | |
| <20 ng/ml (deficiency) | 80/132 (60.6%) |
| 20≤~<30 ng/ml (insufficiency) | 44/132 (33.3%) |
| ≥30 ng/ml (sufficiency) | 8/132 (6.1%) |

Since there is no definite consensus on optimal levels of serum vitamin D, we defined serum 25OHD concentration according to the previous report [26] as following; less than 20 ng/ml; deficient VD level, 20 ng/ml or more and less than 30 ng/ml; insufficient VD level, and 30 ng/ml or more; sufficient VD level. Overall, average serum concentration of 25OHD in 132 patients was 18.1 ng/ml, indicating that RA patients are generally in the VD deficient status. As shown in table 1, 80 patients (60.6%) were regarded as apparent VD deficiency with serum concentration of less than 20 ng/ml, and 44 patients (33.3%) were insufficiency. Only 8 patients (6.1%) were regarded as sufficient VD status showing the level more than 30 ng/ml, which is thought to be effective for bone fracture prevention [27,28].

The clinical characteristics of the patients stratified according to the VD levels, deficiency, insufficiency and sufficiency, were compared (Table 2). Disease activity evaluated by DAS28-CRP or CRP levels was not different among three groups. Serum levels of transaminases, ALP, albumin, Ca and P were also similar in three groups. Only in VD sufficiency group, renal function which was assessed by BUN, serum creatinine or eGFR was slightly impaired as compared to the other groups. We considered, however, that it was difficult to explain the low VD levels found in RA patients by these clinical markers.

Since it was reported that serum 25OHD was associated with a decline in physical activity [29,30], we examined relationship of the 25OHD levels and Steinbrocker's functional class. As expected, serum 25OHD levels showed a significant decrease with the advance in functional impairment (Figure 1A), while 1,25 $(OH)_2D$ levels did not show such a correlation. On the other hand, concentration of these VD metabolites did not correlate with Steinbrocker's radiographic stage (Figure 1B).

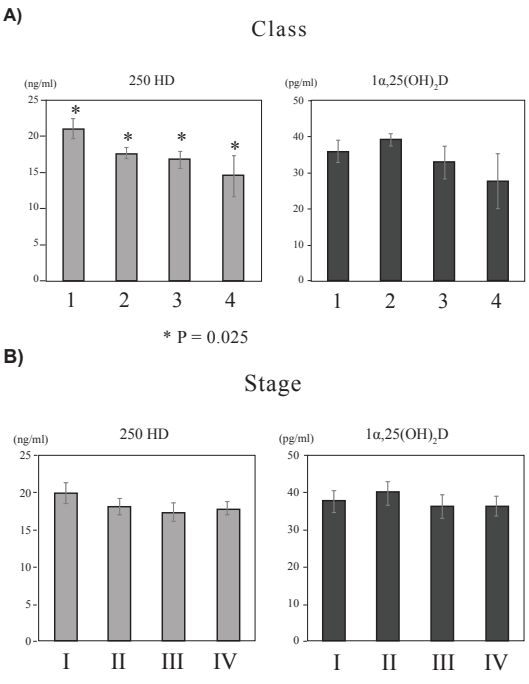


**Figure 1:** Relationship between serum vitamin D levels and Steinbrocker's functional class (A) or Steinbrocker's radiographic stage (B)

**Table 2:** Laboratory parameters of the patients stratified by serum vitamin D levels.

| | All patients (n=132) | 25OHD deficiency <20 ng/ml (n=80) | 25OHD insufficiency 20≤~<30 ng/ml (n=44) | 25OHD sufficiency ≥30 ng/ml (n=8) | p value |
|---|---|---|---|---|---|
| DAS 28-CRP | 2.18 (1.15-6.58) | 2.19 (1.17-6.58) | 2.31 (1.16-6.52) | 1.33 (1.15-3.39) | 0.4314 |
| CRP (mg/dl) | 0.30 (0-6.67) | 0.27 (0-6.67) | 0.35 (0-5.76) | 0.55 (0.14-3.39) | 0.8921 |
| AST (U/l) | 20 (11-97) | 20 (11-79) | 21 (12-97) | 17 (12-23) | 0.2558 |
| ALT (U/l) | 16 (6-135) | 16 (6-89) | 20 (12-135) | 11.5 (8-39) | 0.1129 |
| ALP (mg/dl) | 215 (112-744) | 214 (114-744) | 217 (112-562) | 196 (129-362) | 0.7959 |
| Alb (g/dl) | 3.9 (2.4-5.0) | 3.8 (2.4-5.0) | 3.9 (3.1-4.6) | 4.0 (3.8-4.3) | 0.2456 |
| BUN (mg/dl) | 15.8 (6.8-45.1) | 15.3 (7.1-45.1) | 15.8 (6.8-33) | 20.0 (15.3-28.9) | 0.0536 |
| Cre (mg/dl) | 0.61 (0.32-2.40) | 0.58 (0.32-1.16) | 0.62 (0.33-2.40) | 0.85 (0.49-1.34) | 0.0017 |
| eGFR (ml/min/1.73m$^2$) | 81.1 (15.9-157.1) | 85.0 (36-157.1) | 81.5 (15.9-144.2) | 55.9 (44.8-95.3) | 0.0533 |
| Ca (mg/dl) | 9.0 (8.1-9.9) | 9.0 (8.1-9.9) | 9.0 (8.6-9.8) | 9.3 (8.8-9.8) | 0.1307 |
| P (mg/dl) | 3.2 (2.2-4.9) | 3.2 (2.2-4.9) | 3.3 (2.4-4.2) | 2.4 (2.3-3.0) | 0.0850 |

Median value and the range (parenthesis) are shown.

## Discussion

Systemic and periarticular bone loss is characteristic in RA[3]. From the point of view of bone mineral metabolism, a critical serum 25OHD concentration widely accepted is 20 ng/ml [26]. It is also demonstrated that at least 20ng/ml of serum 25OHD concentration is required for normalization of PTH levels and prevention of decrease in BMD in Japanese postmenopausal women [31]. Sixty % of our RA patients showed less than 20 ng/ml which is a definite VD deficiency, and 33 % had insufficient VD levels. This finding is basically consistent with those in previous reports surveyed in RA patients of different ethnic populations 16-18, although serum 25OHD levels which is defined as deficiency is different in each report (15 to 20 ng/ml). A couple of reports described that 25OHD levels in RA patients were not different from those of controls 19, 20. To our knowledge, there is no report which compares serum VD levels in RA patients and healthy controls in Japanese population. Although there are many undetermined factors which may influence serum VD levels, such as ethnic difference, different lifestyles or seasonal variations of serum 25OHD levels, we showed here that, at least, the majority of RA patients in our clinical setting have low serum levels of 25OHD.

Serum 25OHD concentration became significantly lower as the Steinbrocker's functional class became higher, while serum 1,25$(OH)_2$D levels did not show such a tendency in the present study. The latter result is plausible by the fact that renal production of 1,25 $(OH)_2$D is strictly regulated by PTH, serum calcium and phosphorus levels [26]. It was shown that 25OHD level was negatively correlated with DAS scores and Steinbrocker's functional class [16]. We did not, however, find a correlation between 25OHD levels and DAS scores. Average DAS scores in the three groups stratified by serum 25OHD levels were not significantly different and actually estimated as low disease activity. This finding apparently indicates that serum 25OHD levels are determined by physical activity itself, and not by disease activity. This speculation is fortified by the previous reports. Nakamura et al. [29] demonstrated that very few people had deficient VD levels among active elderly Japanese populations who engaged in outdoor activity in summer study. Wicherts et al. [30] also showed that lower serum 25OHD is associated with a decline in physical performance in elder people.

In the present study, we surveyed patients' VD levels in June, a rainy season in Japan. Although we did not ask the patients' daily lifestyle during the survey, it is surmised that the subjects with physical impairment were likely not to intend to go outside and consequently might get less sunlight or UV exposure. In this regard, there are intriguing reports which showed the effect of sunlight. Thus, approximately 10 min/day sunlight exposure for 1 year increased serum 25OHD levels and BMD in hospitalized elderly women with Alzheimer's disease [32] and also in Parkinson's disease [33]. Although VD supplementation is likely to be reasonable for keeping bone health in RA patients, it has not been proved whether the sunlight effect on VD and BMD could be also expected in RA patients.

Besides the effect on bone mineral metabolism, several physiological effect of VD which could be relevant to RA has been proposed. RA patients, even with low or moderate disease activity (average DAS28=2.15), have preferential reduction of BMD at femoral neck in Japan [4]. Although fractures in RA patients occur at various sites [6], the increased risk of hip fracture in RA patients is also known [34]. A decrease in femoral neck BMD is apparently associated with reduced ADL of the patients, and is attributed to low muscle tonus [4]. In this regard, a meta-analysis demonstrated that VD supplementation reduce the risk of falls [14]. It known that active form of VD improves muscle function through VD receptors in muscle cells [35,36].

Various lines of evidence showed the effect of VD on immune function. However, TNFα or B cells which are dominantly involved in RA pathophysiology do not directly influence serum 25OHD levels. Thus, it was reported that adalimumab (anti-TNFα antibody) or rituximab (anti-CD20 antibody) improved the disease activity while such treatments did not change 25OHD levels [17, 37].

In the present study, we found high prevalence of VD deficiency

in RA patients, in particular, those with low physical activity. This finding is consistent with the reports from different ethnic populations. Therefore, clinicians should keep in mind that VD deficiency is a general and important characteristic of RA although it is not apparent as a clinical symptom. Considering versatile actions of VD, VD supplementation including sunlight exposure could be beneficial for long term management of RA patients to improve their quality of life, although this surmise should be further investigated.

## Disclosure of Conflict of Interest

The authors have no conflict of interest which should be disclosed.

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