The Relationship of Serum Vitamin D Level and Disease Activity in Rheumatoid Arthritis Patients

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Background: *The inverse correlation of serum vitamin D (25 (OH) D) level and disease activity in patients with rheumatoid arthritis (RA) is not consistently documented across different ethnic groups.*
Objective: *To investigate the relationship of 25 (OH) D level with disease activity and functional ability in Thai patients with RA.*
Material and Method: *Between June, 2012 and December,2012 90 RA patients were enrolled from the outpatient department of Thammasat University Hospital, Pathumthani, Thailand. 25 (OH) D concentrations were measured and the disease activity score 28 (DAS-28) and Thai health assessment questionnaire (Thai HAQ) were assessed. Based on the DAS-28, patients were divided into three groups: (i) low ≤3.2, (ii) moderate >3.2 to 5.1, and (iii) severe >5.1. 25 (OH) D level were compared among groups.*
Results: *Of 90 patients, 20 (22.2%) and 48 (53.3%) were vitamin D deficiency (25 (OH) D ≤20 ng/ml) and insufficiency (25 (OH) D >20 to 30 ng/ml), respectively. The mean 25 (OH) D concentration was 25.6±6.9 ng/ml. There was no significant difference in serum vitamin D among three groups (p = 0.20). Neither disease activity nor functional ability was correlated with serum vitamin D level (p = 0.98 and 0.93 respectively).*
Conclusion: *Most of rheumatoid arthritis patients had inadequate serum vitamin D. There was no correlation between serum vitamin D level and disease activity and functional ability.*

Keywords: *Serum vitamin D, Rheumatoid arthritis, Disease activity score*

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Vitamin D, also known as 1,25-Dihydroxy vitamin D_3 (1, 25 $(OH)_2 D_3$) is a secosteroid hormone that has an important role in calcium metabolism and regulating immune responses by enhancing innate immune function and down regulating the adaptive immune response[1,2]. The immunomodulatory effect is mediated via vitamin D receptor (VDR) which are expressed in neutrophils, macrophages, dendritic cells, T and B lymphocytes. Regarding innate immunity, vitamin D promotes the differentiation of monocytes into macrophages and enhances the chemotaxis and cytokine secretion during infection[3]. In contrast, it inhibits the differentiation, maturation, antigen processing and presentation of dendritic cells[4]. Vitamin D also suppresses Th1 function[5], Th17 differentiation[6], interleukin-17 (IL-17) production, B-cell proliferation and differentiation[7] but induces regulatory T cells (T reg), interleukin-4 (IL-4), and interleukin-10 (IL-10) productions[8]. Vitamin D insufficiency/deficiency is associated with an increased risk of developing several autoimmune diseases such as multiple sclerosis, inflammatory bowel disease and type I diabetes[9-11]. Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic destructive joint inflammation. In a mouse model of collagen-induced arthritis, treatment with 1, 25 $(OH)_2 D_3$ inhibited early inflammatory process[12]; another study showed that the VDR agonist also reduced inflammation in late stage arthritis[13]. Furthermore, 1, 25 $(OH)_2 D_3$ controls human rheumatoid synovial fibroblasts and chondrocytes in synthesis of matrix metalloproteinase and prostaglandin E_2[14]. The prevalences of vitamin D deficiency in RA patients were 43, 48.85, 52, and 71.8% in US, Chinese, Italian, and Japanese population, respectively[15-18]. An inverse

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association between serum 25 (OH) D level and disease activity was reported in some studies[19-28] but the inconsistent outcome was found in others[29-33]. Furthermore, the results among middle east countries were still conflicting[25,27,30,32]. In Thailand, Pakchotanon et al showed that there was no correlation between serum 25 (OH) D and disease activity[34]. The present study was performed to assess the relationship of serum vitamin D level and disease activity in Thai patients with confirmed RA.

Material and Method

This observational study was conducted at the Rheumatology Outpatient Department of Thammasat university hospital between June 1, 2012 and December 31, 2012. All patients were aged ≥18 years and fulfilled the 1987 American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis and gave freely written informed consent. The study was approved by the ethics committee of Faculty of Medicine, Thammasat University. Data were collected onto a standard case record form (CRF) and included age, gender, body mass index (weight/height^2), education level, occupation, smoking, alcoholic intake, disease duration, other medical illnesses and medications. A physical examination was done and the number of tender and swollen joints documented. Patients were asked to self-assess their pain and global health by visual analogue score (VAS) and to complete Thai Health Assessment Questionnaire Disability Index (Thai HAQ). Blood was obtained to measure 25 (OH) D concentration by chemiluminescent immunoassay (CLIA) Abbott Co., USA and the erythrocyte sedimentation rate (ESR). DAS28 was calculated. Based on the DAS28, RA disaesa activity was classified as low (DAS28 ≤3.2), moderate (DAS28 >3.2 to 5.1), or severe (DAS28 >5.1). Vitamin D insufficiency and deficiency were classified as serum 25 (OH) D concentrations of ≤20 and >20 to 30 ng/mL, respectively.

Statistical analysis was done by using SPSS version 11.0. One way ANOVA and Chi-square test were used to compare continuous and categorical variables among groups. Bivariate correlations of continuous data were analyzed by Pearson's correlation. Factors associated with serum 25 (OH) D concentrations were explored by multivariate analysis. The *p*-value <0.05 was considered statistical significance.

Results

Ninety RA patients were recruited of mean age was 51.8±12.2 (17 to 75) years (Table 1). 83 (92.2%) patients were women. The majority of patients (n = 80) lived in rural area whose education level was high school. Approximately one-third were housewives, and few either smoked or drank alcohol. Hypertension, diabetes mellitus, and dyslipidemia were not common. The mean disease duration was 82.8±79.2 (3.6 to 480)

Table 1. Characteristics of patients

Characteristics	Number (%)
Gender	
Female	83 (92.2)
BMI (kg/m^2)	
<18.5 to 22.9	42 (46.6)
23 to 24.9	16 (17.7)
25 to 29.9	24 (26.6)
≥30	8 (8.8)
Education	
Elementary	43 (47.8)
Secondary	9 (10.0)
High School	12 (13.3)
Diploma and bachelor's degree	26 (28.9)
Occupation	
Housewife	32 (35.6)
Trader	26 (28.9)
Employee	13 (14.4)
Official	10 (11.1)
Farmer	6 (6.7)
Student	3 (3.3)
Smoking	
Non-smoker	85 (94.4)
Ex or current smoker	5 (5.5)
Alcoholic drinking	
Non-drinker	78 (86.7)
Ex or current drinker	12 (13.3)
Medical illness	
Diabetes mellitus	19 (21.1)
Hypertension	19 (21.1)
Dyslipidemia	11 (12.2)
Rheumatoid arthritis	
Rheumatoid nodule	2 (2.2)
RF positive	45 (50)
Anti-CCP positive	69 (76.7)
RF and anti-CCP positive	34 (37.7)
Measurement	Mean (SD)
Tender joint count	2.3 (±3.1)
Swollen joint count	3 (±2.9)
ESR (mm/hr)	39 (±22.6)
Patient's global assessment of health (0 to 100)	40.2 (±22.2)
Pain (0 to 100)	34.1 (±23.6)
DAS28	4.0 (±1.2)
HAQ	0.6 (±0.6)

months. 45 (50%), 69 (76.7%), and 34 (37.7%) patients were RF positive, anti-CCP positive, and positive for both tests, respectively. Clinically, only two patients had rheumatoid nodules. Means (SE) of the tender and swollen joint count were 2.3±3.1 and 3±2.9. Patients's average pain score was 34.1±23.6. Regarding the assessment of patients, means of DAS28 and HAQ score were 4.0±1.2 and 0.6±0.6.

There were consecutively 55 (61.1%) and 35 (38.8%) patients treated with ≤2 and ≥3 types of DMARDs and only 2 patients were received biologic agents. Methotrexate, known as the first line drug for rheumatoid arthritis, was prescribed in almost all of the patients (91.1%). Sulfasalazine hydroxychloroquine, and leflunomide were used in 55.6, 34.4, and 31.5% of the patients, respectively. The other DMARDs (azathioprine, cyclosporine, cyclophosphamide) were used only in 10%. Almost half of the patients (46.6%) took prednisolone at mean dosage 14.5±20.1 (0 to 70) mg/week. Vitamin D and calcium supplement were given to 31 (34.4%) and 43 (47.8%) patients, respectively. Of 90 patients, 68 (75.5%) had low serum 25 (OH) D level (<30 ng/mL) and mean serum vitamin D was 25.6±6.9 (13.9 to 42.2) ng/mL. Low, moderate, and high disease activity scores were found in 28 (31.1%), 43 (47.8%), and 19 (21.1%) patients, respectively (Table 2). Comparing of three DAS28 groups, there were no significant differences in age, BMI, rheumatoid factor, anti-CCP, and serum vitamin D concentrations (Table 3). However, the mean dose of prednisolone was significantly higher in severe disease activity group. There were no correlations between serum vitamin D concentrations and disease activity scores and other tested factors (Table 4).

Discussion

The present study has shown that Thai RA patients have commonly vitamin D deficiency (~20%) and insufficiency (~50%). The comparatively lower rate of vitamin D deficiency is probably explained by increased sun exposure in rural dwellers. Additionally, ~30% of the patients have received vitamin D2 supplement 400-800 IU/day. However, this formulation of vitamin D2 is not sufficient for most patients. They still have vitamin D deficiency (12.9%) and insufficiency (64.5%). Other studies, from both western and eastern countries, have documented higher rates of vitamin D deficiency of between 40 to 70%[15-18,29]. We did not

Table 2. Disease activity status, serum vitamin D level, and treatment

	Number (%)
DAS28	
Low disease activity (≤3.2)	28 (31.1)
Moderate disease activity (>3.2 to 5.1)	43 (47.8)
Severe disease activity (>5.1)	19 (21.1)
Serum vitamin D level (ng/mL)	
Vitamin D deficiency (≤20)	20 (22.2)
Vitamin D insufficiency (>20 to <30)	48 (53.3)
Normal vitamin D (≥30)	22 (24.4)
Number of DMARDs medication	
0 to 1	19 (21.1)
2	36 (40)
3	26 (28.8)
4	9 (10)
Prednisolone	42 (46.6)
Vitamin D supplement	31 (34.4)
Calcium supplement	43 (47.8)

Table 3. Comparison of serum vitamin D level in three disease activity groups

	Low disease activity (n = 28)	Moderate disease activity (n = 43)	Severe disease activity (n = 19)	*p*-value
Age,y	50.2±13.8	52.7±11.6	52.4±11.4	0.67
BMI (kg/m^2)	23.7±4.2	24.0±4.5	23.8±4.3	0.94
RF positive	12 (42.8%)	22 (51.2%)	11 (57.9%)	0.58
Anti-CCP positive	20 (71.4%)	32 (74.4%)	17 (89.5%)	0.32
Anti-CCP level (IU/mL)	136.8±144.5	230.2±199.1	165.7±179.2	0.09
Serum vitamin D level (ng/mL)	27.1±7.4	24.3±6.6	26.5±6.9	0.20
Number of patients received vitamin D supplement	8 (28.8%)	17 (32.1%)	6 (31.6%)	0.73
Number of patients treated with prednisolone	9 (32.1%)	21 (48.8%)	12 (63.2%)	0.10
Prednisolone dosage (mg/week)	7.8±16.1	14.5±19.8	24.2±23.1	0.02

Table 4. Correlation between serum vitamin D and variable factors

Variable factors	Serum vitamin D (r)	*p*-value
Age	0.147	0.17
BMI	-0.073	0.492
Duration of disease	0.024	0.82
Tender joint count	0.048	0.65
Swollen joint count	0.014	0.89
Patient's global assessment	-0.049	0.65
Pain assessment	-0.108	0.31
HAQ	0.01	0.93
DAS28	0.001	0.98
ESR	0.033	0.75
Rheumatoid factor	0.093	0.39
Anti-CCP	-0.013	0.90
Prednisolone	0.009	0.93
Vitamin D supplement	0.05	0.64

find an inverse relationship between concentrations of 25 (OH) D and RA disease activity, as assessed by the DAS28 score, as well as clinical markers of disease. These findings agree with previous studies[29-33], including one from Thailand[34] but contrast with others[15,16,19-28]. Cutolo et al[10] found that serum 25 (OH) D level was negatively associated with DAS28 in RA patients from North and South Europe. Hong Q et al[24] reported an inverse relationship with the number of swollen and tender joints, pain score, duration of morning stiffness, HAQ, DAS28 scores and ESR in Chinese RA patients. By contrast, a number of studies[29-34] found no correlation between serum 25 (OH) D and disease activity in different ethnic groups including Caucasian, African American, Turkish, and Japanese. The conflicting results might be caused by many different factors including ethnicity, study design, sample size, clinical heterogeneity, and analytical methods. Recently, there have been two meta-analysis studies[35,36] showing the similar outcomes. Vitamin D deficiency is more prevalent in RA patients than healthy controls and serum 25 (OH) D concentration is negatively associated with disease activity. Moreover, this relationship is stronger in low-latitude areas, especially in developing countries[35].

The role of vitamin D as an immunomodulator in autoimmune diseases including RA was well recognized. However, the inconsistency in studies between serum 25 (OH) D concentrations and clinical and inflammatory markers of disease activity make it difficult to define the immunoregulatory role of 25 (OH) D in RA. In terms of vitamin D supplement and disease activity, there was only one exploratory study showed that a 3-month vitamin D supplement improved disease activity. Therefore, a double-blind randomized control trial is needed to validate this result. Variations in 25 (OH) D concentrations may be due to multiple factors such as host genetics, body mass index, geographical area and sunlight exposure.

This study had several limitations. It was a comparatively small observational study in RA patients only that may have been under powered for some of the analyses.

Conclusion

This study has confirmed that vitamin D insufficiency and deficiency are not uncommon in rheumatoid arthritis patients but these did not inversely correlate with disease activity. The awareness of these conditions should be emphasized in patient care. A long-term prospective study should be performed to evaluate the association between serum 25 (OH) D level and disease activity and document any beneficial effects on prognosis.

What is already known about this topic?

Vitamin D deficiency is common in RA patients both in Western and Eastern countries, including Asia. However, the inverse association between serum 25 (OH) D level and disease activity are inconsistent among different population. The previous study showed that there was no correlation in Thai RA patients.

What this study adds?

Vitamin D deficiency is not uncommon in Thai RA patients. The present study confirmed that there

was no inverse relationship between serum 25 (OH) D and disease activity in Thai RA patients, including from rural area.

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Potential conflicts of interest

None.

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ความสัมพันธ์ของระดับวิตามินดีและสถานะระดับอาการของโรคในผู้ป่วยโรคข้ออักเสบรูมาตอยด์

พันธุ์จง หาญวิวัฒนกุล, จิรวรรณ สิงเห

ภูมิหลัง: *การศึกษาก่อนหน้านี้พบว่าระดับวิตามินดีนั้นสัมพันธ์กับสถานะระดับอาการของโรคในผู้ป่วย โรคข้ออักเสบรูมาตอยด์แต่ละเชื้อชาติมีความแตกต่างกัน*

วัตถุประสงค์: *เพื่อศึกษาความสัมพันธ์ของระดับวิตามินดีกับสถานะระดับอาการของโรคและความสามารถ ในการทำงานของผู้ป่วยโรคข้ออักเสบรูมาตอยด์ชนชาติไทย*

วัสดุและวิธีการ: *ผู้ป่วยข้ออักเสบรูมาตอยด์ที่มารับการรักษาที่แผนกผู้ป่วยนอกโรงพยาบาลธรรมศาสตร์ เฉลิมพระเกียรติระหว่างเดือนมิถุนายน ถึงเดือนธันวาคม พ.ศ. 2555 จำนวน 90 ราย ได้รับการเจาะเลือดตรวจระดับวิตามินดี ประเมินสถานะระดับอาการของโรคและสอบถามประเมินสุขภาพ จากนั้นแบ่งกลุ่มผู้ป่วยเป็น 3 กลุ่ม ตามสถานะระดับอาการของโรค คือ กลุ่มที่ 1 ระดับการกำเริบน้อย คะแนนตั้งแต่ 3.2 หรือน้อยกว่า กลุ่มที่ 2 ระดับการกำเริบปานกลาง คะแนนมากกว่า 3.2 แต่ไม่เกิน 5.1 และกลุ่มที่ 3 ระดับการกำเริบรุนแรง คะแนนมากกว่า 5.1 และทำการเปรียบเทียบระดับวิตามินดีระหว่างกลุ่ม*

ผลการศึกษา: *ในจำนวนผู้ป่วย 90 ราย พบภาวะขาดวิตามินดี 20 ราย (22.2%) และ 48 ราย (53.3%) มีภาวะวิตามินดีไม่เพียงพอ (ค่าระดับวิตามินดี ≤20 นาโนกรัม/มิลลิลิตร และ >20 ถึง 30 นาโนกรัม/มิลลิลิตร ตามลำดับ) ค่าเฉลี่ยระดับวิตามินดีอยู่ที่ 25.6±6.9 นาโนกรัม/มิลลิลิตร พบว่าไม่มีความแตกต่างของระดับวิตามินดีในผู้ป่วยทั้งสามกลุ่ม ($p = 0.20$) และระดับวิตามินดีไม่มีความสัมพันธ์กับทั้งสถานะระดับอาการของโรคและความสามารถในการทำงานของผู้ป่วย ($p = 0.98$ และ 0.93 ตามลำดับ)*

สรุป: *ผู้ป่วยโรคข้ออักเสบรูมาตอยด์ส่วนใหญ่มีภาวะพร่องวิตามินดี แต่ระดับวิตามินดีไม่มีความสัมพันธ์กับสถานะ อาการของโรครวมถึงความสามารถในการทำงานด้วย*