



# Comparison of vitamin D profile between patients with inflammatory and non-inflammatory rheumatic diseases

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## ABSTRACT

**Aims:** The aim of this study was to compare serum vitamin D levels in patients with inflammatory rheumatic diseases and non-inflammatory musculoskeletal disorders presenting with pain.

**Methods:** Patients were divided into three groups. Group 1 consisted of patients with inflammatory rheumatic diseases; group 2, non-inflammatory musculoskeletal disorders; and group 3, healthy controls. The plasma levels of 25(OH)D <10 ng/mL were accepted as vitamin D insufficiency. Correlation between pain intensity (visual analog scale), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, disease activity score 28 (DAS28)-CRP for rheumatoid arthritis patients, Bath Ankylosing Spondylitis Disease Activity Index for ankylosing spondylitis patients, and 25(OH)D levels were analyzed.

**Results:** Eighty-one patients with inflammatory rheumatic diseases (group 1, mean age=47.8±12.2 years), 26 patients with non-inflammatory musculoskeletal disorders (group 2, mean age=46.6±4.5 years), and 36 healthy controls (group 3, mean age=45.2±9.2 years) were included. There was a significant difference among the groups regarding 25(OH)D levels (group 1=16.4±11.3 ng/mL, group 2=13.9±6.4 ng/mL, group 3=20.4±8.2 ng/mL) (p=0.031). 25(OH)D levels in patients with non-inflammatory musculoskeletal diseases were lower than the healthy controls (p=0.003). No significant difference was seen between two patient groups (p=0.334). There was a weak-to-moderate negative correlation between pain intensity, ESR, CRP, DAS28-CRP and 25(OH)D levels (r=-0.302, p=0.002; r=-0.259, p=0.020; r=-0.259, p=0.020; r=-0.374, p=0.022 respectively).

**Conclusions:** The results of this study are important in terms of routine monitoring and replacement of vitamin D in case of deficiency in chronic inflammatory and non-inflammatory rheumatic diseases presenting with pain.

## Introduction

Vitamin D is synthesized in the skin in the presence of sunlight and then metabolized into an active metabolic form in the liver, kidney and peripheral immune/inflammatory cells. Active metabolite of vitamin D [1,25(OH)<sub>2</sub>D] is important for bone metabolism and function of neuromuscular system. The deficiency of this hormone is mainly associated with osteoporosis in adults and rickets in pediatric population. Also, the deficiency of this hormone is observed to be associated with different forms of non-inflammatory chronic pain conditions (1-4). One of the types of non-inflammatory chronic pain is persistent nonspecific musculoskeletal pain, such as non-inflammatory unexplained

arthralgia or myalgia, which is seen frequently in rheumatology clinics. In this type of chronic pain conditions, reaching a precise diagnosis and decision on an effective treatment can be quite challenging for the clinician.

Vitamin D is also known to have a role in the regulation of immune system. Active metabolite of vitamin D appears to have an immunosuppressive effect and to play a role in the autoimmune diseases (5). It is not so evident that the deficiency of vitamin D has causality for rheumatic diseases, whereas the prevalence is claimed to be high (6-8). Several surveys indicated that patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), scleroderma, polymyositis, dermatomyositis and systemic lupus

erythematosus had lower levels of 25(OH)D than the healthy population (6,7). Also, there are a number of studies in which vitamin D was reported to be related to the disease activity in patients with inflammatory rheumatologic diseases (9-11). Among these, two of the mostly studied rheumatologic diseases are RA and AS. The initiation and progression of these diseases have been thought to be associated with the plasma values of vitamin D (12).

To the best of our knowledge, no comparative analysis of serum vitamin D exists between inflammatory and non-inflammatory musculoskeletal diseases. The primary aim of this study was to investigate plasma vitamin D levels among patients with inflammatory rheumatic diseases and those with non-inflammatory musculoskeletal disorders who presented with pain, and to compare vitamin D levels with healthy controls. The secondary aim was to determine the relationship between disease activity of inflammatory rheumatologic diseases and vitamin D levels.

## Methods

### Subjects

This retrospective case-control study was conducted between the dates of December 2015 and March 2016. Patients with inflammatory and non-inflammatory rheumatic diseases along with the healthy controls, who were referred to the physical medicine and rehabilitation outpatient clinic, were retrospectively screened up to the date of January 2009.

Group 1 consisted of patients with inflammatory rheumatic diseases including RA and AS. The diagnoses of RA and AS were based upon the 2010 ACR/EULAR criteria and 1984 modified New York criteria, respectively.

Group 2 included the patients with non-inflammatory musculoskeletal disorders, such as unexplained myalgia, bone pain and arthralgia without tenderness, erythema, limitation of motion or swelling persisting for more than three months, which could not be attributed to any precise disease based on clinical, radiographic and laboratory examinations.

Group 3 was comprised of healthy controls.

Patients with fibromyalgia, osteoarthritis, chronic kidney and/or liver disease, malignancy, inflammatory rheumatic diseases other than RA and AS, malabsorption syndromes, pregnancy, and individuals who were on corticosteroid regimen or vitamin D supplementation were excluded from the study.

### Measurements

All descriptive, clinical and laboratory data were recruited from the hospital database. Pain levels which were measured with visual analog scale (VAS); tender and swollen joint counts (SJC); disease activity, which was recorded as disease activity score 28 (DAS28)-C-reactive protein (CRP)

score for RA and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score for AS, were obtained from patients' medical records.

The baseline 25(OH)D levels prior to any vitamin D supplementation, which were measured with the high performance liquid chromatography technique using chromo system kit, were noted. The plasma levels of 25(OH)D >30 ng/mL were considered as optimal vitamin D status, whereas levels <10 ng/mL were accepted as vitamin D insufficiency (13). Concurrent erythrocyte sedimentation rate (ESR) and CRP levels of the patients with inflammatory rheumatic diseases were also documented.

### Statistical Analysis

Data evaluation was conducted with Statistical Package for the Social Sciences (SPSS) 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics was performed to calculate mean and standard deviation, median and range values. Normality of the variables was checked by the Kolmogorov-Smirnov Test. Two group comparisons and multiple group comparisons were performed via the Mann-Whitney U and Kruskal-Wallis tests, respectively. Values are given as mean ( $\pm$ standard deviation). The Spearman correlation analysis was used in order to evaluate the associations between variables. The correlation coefficient (r) value of 0-0.24 was considered as "no correlation", 0.25-0.49 as "weak", 0.5-0.74 as "moderate", and 0.75-1 as "strong" correlation.  $P < 0.05$  was considered as statistically significant.

Ethical approval of the study was obtained from the Cukurova University Faculty of Medicine Local Ethics Committee (protocol number: 2014/34).

## Results

Eighty-one patients with inflammatory rheumatic diseases (group 1, mean age=47.8 $\pm$ 12.2 years), 26 patients with non-inflammatory musculoskeletal disorders (group 2, mean age=46.6 $\pm$ 4.5 years) and 36 healthy controls (group 3, mean age=45.2 $\pm$ 9.2 years) were included in the study. The demographic, clinical and laboratory results of the patients are summarized in Table 1.

The mean 25(OH)D levels were measured as 16.4 $\pm$ 11.3 ng/mL in group 1 (15.51 $\pm$ 12.15 ng/mL in RA patients, 40.63 $\pm$ 9.29 in AS patients), 13.9 $\pm$ 6.4 ng/mL in group 2, and 20.4 $\pm$ 8.2 ng/mL in group 3. According to one-way ANOVA test, 25(OH)D levels significantly differed among three groups ( $p=0.031$ ). In post-hoc analysis, the level of vitamin D in the non-inflammatory musculoskeletal disease group was statistically significantly lower than in the healthy control group ( $p=0.003$ ), whereas there was no statistically significant difference between the inflammatory disease group and other groups (group 1-2,  $p=0.334$ ; group 1-3,  $p=0.087$ ). The percentages of vitamin D

**Table 1. Demographic, clinical and laboratory characteristics of the groups**

	Group 1	Group 2	Group 3	p#
Rheumatoid arthritis	Ankylosing spondylitis	Non-inflammatory musculoskeletal pain	Healthy control	
Age (years) (mean ± SD)	54.78±10.46	40.63±9.29	46.58±4.53	45.23±9.223 0.473
Gender [female (%)]	39 (95.1%)	22 (55%)	19 (73.1%)	18 (51.4%) 0.034*
Vitamin D levels (mean ± SD) (ng/mL)	15.51±12.15	17.31±10.39	13.869±6.439	20.41±8.22 0.031*
Sedimentation rate (mean ± SD) (mm/h)	32.00 (20.00-45.50)	24.50 (11.00-36.50)	-	-
CRP (mean ± SD) (mg/dL)	0.80 (0.30-1.93)	0.73 (0.37-1.76)	-	-
RF (mean ± SD) (IU/mL)	22.40 (20.00-55.60)	20.75 (20.00-21.50)	-	-
DAS28-CRP	3.16±1.59	-	-	-
BASDAI score	-	3.69 (2.70-5.82)	-	-
PTH levels (mean ± SD) (pg/mL)	51.22±34.26	47.49±32.40	60.28±32.40	-
Calcium levels (mean ± SD) (mg/dL)	9.28±0.43	9.24±0.51	8.90±0.53	-
ALP [median (25-75)] (U/L)	64.0 (55.0-85.0)	67.0 (56.0-88.5)	69.0 (58.0-91.5)	-
SJC n, [median (25-75)]	0.0 (0.0-2.5)	-	-	-
TJC n, [median (25-75)]	1.5 (0.0-6.5)	-	-	-
VAS n, [median (25-75)]	5.00 (2.00-7.00)	4.00 (3.00-6.75)	4.00 (3.00-5.25)	-
Medication	NSAID n, %	3 (7.3%)	12 (30%)	-
	B.DMARD n, %	3 (7.3%)	10 (25%)	-
	S.DMARD n, %	35 (85.4%)	18 (45%)	-

\*P<0.05 is considered statistically significant.  
#P values represent for the comparisons between 3 groups (group 1, group 2, group 3).  
SD: Standard deviation, CRP: C-reactive protein, RF: Rheumatoid factor, DAS28-CRP: Disease activity score for rheumatoid arthritis, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, PTH: Parathyroid hormone levels, ALP: Alkaline phosphatase, SJC: Swollen joint count, TJC: Tender joint count, VAS: Visual analog scale, NSAID: Non-steroidal anti-inflammatory drugs, B.DMARD: Biological disease modifying anti-rheumatic drugs, S.DMARD: Synthetic disease modifying anti-rheumatic drugs

insufficiency [25(OH)D <10 ng/mL] in group 1 (RA/AS), 2 and 3 were 29.7% (39%/25%), 23.1% and 8.6%, respectively.

VAS values were found to be similar in RA, AS, and non-specific musculoskeletal pain patients (p=0.720). Vitamin D levels had no difference between female (17.01±11.15 ng/mL) and male (17.74±7.03 ng/mL) patients (p=0.862).

We found weak-to-moderate negative correlation between VAS, SJC, ESR, CRP, DAS28-CRP and 25(OH)D levels (r=-0.302, p=0.002; r=-0.389, p=0.045; r=-0.259, p=0.020; r=-0.259, p=0.020; r=-0.374, p=0.022; respectively). No correlation was found between vitamin D levels and BASDAI scores (p=0.913) (Table 2).

## Discussion

The findings of the study revealed that i) patients with non-inflammatory musculoskeletal conditions had significantly lower vitamin D levels when compared to the patients with the inflammatory diseases and the healthy controls, ii) vitamin D had a weak correlation with inflammatory markers and disease

**Table 2. Correlation analysis between pain, inflammation markers, disease activity indexes and 25(OH)D levels**

25(OH)D levels	r	p
Visual analog scale (pain)	-0.302	0.002*
Swollen joint count	-0.389	0.045*
Erythrocyte sedimentation rate	-0.259	0.020*
CRP	-0.259	0.020*
Disease Activity Score 28-CRP	-0.374	0.022*
Bath Ankylosing Spondylitis Disease Activity Index	-0.214	0.913

\*p<0.05 is considered as statistically significant.  
CRP: C-reactive protein

activity parameters in patients with inflammatory rheumatic diseases and also with pain intensity in all groups.

Both genetic and environmental factors play a role in the pathophysiology of rheumatic diseases. As an environmental compound, the deficiency of vitamin D appears to be associated with the initiation and progression of the disease in patients

with both RA and AS. A study conducted in the Asian region demonstrated that 65% of the RA patients had vitamin D levels below 30 ng/mL (14). Sahebari et al. (15) showed low levels of vitamin D even among the early-diagnosed RA patients. Furthermore, Merlino et al. (16) suggested that vitamin D supply to RA patients had an impact on lowering the incidence of RA. Similar to RA patients, studies conducted on AS patients have shown that low serum vitamin D profile is a common finding in also AS population. Zhao et al. (17), in their systemic review, addressed several cross-sectional studies, which revealed that AS was related to low vitamin D concentrations. Also, a recent meta-analysis has showed that the activation of AS is inversely correlated with 25(OH)D levels and higher serum vitamin D concentrations might decrease the risk of AS (18).

Our results are consistent with the general opinion that low vitamin D levels are commonly seen in inflammatory rheumatic diseases even if it has no statistical significance when compared to the healthy controls. Additionally, the results also indicated that vitamin D level was also significantly lower in patients with non-inflammatory musculoskeletal conditions. We additionally found that vitamin D levels were weakly correlated to inflammatory markers, disease activity in rheumatic conditions and pain intensity in all groups. These findings raise a number of questions: Is the vitamin D deficiency in inflammatory rheumatic diseases independent from inflammation? Is there a common mechanism that explains the decrement of vitamin D in inflammatory and non-inflammatory rheumatic conditions?

There are several observational studies suggesting an association between vitamin D levels and inflammatory markers (19,20). However, these studies are mostly on specific patient groups; thus, it cannot be generated to all population. According to a review written by da Silva and Rudkowska (20), studies investigating the association of vitamin D with inflammatory markers have conflicting results. According to a meta-analysis in RA patients, serum vitamin D level was found to be significantly low in patients with RA, vitamin D deficiency was prevalent in RA patients compared to controls, and the vitamin D level correlated inversely with RA activity (21). However, a recent study showed opposite results in which they found similar levels of 25(OH)D levels in the RA patients with age- and gender-matched healthy controls, and no association with joint damage and disease activity (22). Similarly, the studies in AS are not completely in agreement about a possible relation between poor vitamin disease activity parameters and serum vitamin D levels (23). In our study, we found a weak correlation of vitamin D with disease activity in RA, whereas no correlation was found with disease activity of AS patients. One should remember that pain is the common component of disease activity indexes and affects patients' global health. Therefore, it can raise the question whether the relation might be caused by this component rather than the inflammation itself.

There is little evidence in the literature regarding the relationship between vitamin D deficiency and non-inflammatory musculoskeletal conditions (24-26). Again, pain-being the common ground of all these conditions emerges as a variable, which might explain the relation of vitamin D with both non-inflammatory and inflammatory musculoskeletal diseases. Verifying this theory, a study conducted on patients with non-specific musculoskeletal pain showed that vitamin D deficiency was as high as 95.4% and pain responded to vitamin D supplementation in majority of the vitamin D deficient patients (27). According to a review published in 2015, vitamin D was believed to have beneficial effect over placebo in chronic pain (28). In the study of Kumar et al. (29), in which they investigated the vitamin D levels in non-inflammatory musculoskeletal complaints, they found low vitamin D level was frequently the sole cause of polyarthralgia, myalgia, bone pain and chronic widespread pain in patients. In their study, they also observed 75% low vitamin D levels in healthy population. Similar results were reached in the study of Plotnikoff and Quigley (4), where they showed severe hypovitaminosis D in patients with non-specific musculoskeletal pain. In our study, we observed vitamin D deficiency in both inflammatory and non-inflammatory painful rheumatic conditions, but significantly lower vitamin D levels in non-inflammatory musculoskeletal conditions referring to rheumatology clinics with chronic pain. All these studies including the present study confirm the impact of vitamin D on the pathophysiology of pain. Vitamin D can modulate neuronal excitability, play a role in astrocyte detoxification, limit macrophage colony stimulating factor, and decrease macrophage induced inflammation; thus, has a potential of inhibiting pain formation (24,28).

The strong points of the present study are; i) comparing the vitamin D levels in both inflammatory and non-inflammatory musculoskeletal conditions with healthy controls, ii) being able to record the baseline 25(OH)D levels prior to any vitamin D supplementation therapy, and ii) having enough sample size to allow between group comparisons. However, several limitations exist, as well. As a result of its retrospective design, confounders of vitamin D deficiency (such as, daily exposure to sunlight, physical activity level etc.) could not be obtained from the database. There was a gender difference between the groups; albeit, the vitamin D levels were similar between female and male patients.

## Conclusion

In conclusion, low vitamin D level is common in both inflammatory and non-inflammatory rheumatic diseases. Thus, routine monitoring and optimization of vitamin D might be beneficial in all patients presenting with pain. Future prospective trials taking all confounders of vitamin D into account are needed in order to confirm the results of this study.

## Ethics

**Ethics Committee Approval:** Ethical approval of the study was obtained from Cukurova University Faculty of Medicine Ethics Committee (protocol number: 2014/34).

**Informed Consent:** Retrospective case-control study.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: N.C., İ.C.B., S.B., T.S., Concept: N.C., İ.C.B., S.B., T.S., Design: N.C., İ.C.B., S.B., T.S., Data Collection or Processing: N.C., İ.C.B., S.B., T.S., Analysis or Interpretation: N.C., İ.C.B., S.B., T.S., Literature Search: N.C., İ.C.B., S.B., T.S., Writing: N.C., İ.C.B., S.B., T.S.

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