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ARTÍCULOS ORIGINALES / *Originals*

NEGATIVE ASSOCIATION BETWEEN 25-HYDROXYVITAMIN D AND INFLAMMATORY MARKERS IN RHEUMATOLOGIC DISEASES

María Lorena Brance[1,2,3], Maria Silvia Larroudé[4], Guillermo Berbotto[5], Mónica P. Sacnun[6], Carolina Aeschlimann[6], Mariano Palatnik[7], Ignacio Chavero[1], Ariel Sánchez[8], Lucas R. Brun[2,3]

1. Reumatología y Enfermedades Óseas, Rosario. 2. Laboratorio de Biología Ósea. Facultad de Ciencias Médicas. Universidad Nacional de Rosario. 3. National Council of Scientific and Technical Research (CONICET). Argentina. 4. Centro Rossi, Buenos Aires. 5. Sanatorio Británico, Rosario. 6. Hospital Provincial, Rosario. 7. Centro de Reumatología, Rosario. 8. Centro de Endocrinología, Rosario. Argentina

Abstract

Objective

The main purpose of this study was to evaluate serum 25-hydroxyvitamin D (25OHD) levels and its association with inflammatory markers in patients with rheumatologic diseases (RD).

Methods

A cross-sectional study in 154 women with RD (rheumatoid arthritis, spondyloarthritis and other connective tissue diseases) and 112 healthy individuals as a control group (CG) was carried out.

Results

No differences in serum and urine calcium, serum phosphate, and urinary deoxypyridinoline were found. RD group had lower 25OHD and higher PTH compared to CG. RD group had higher C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) compared to CG. The overall mean level of 25OHD (ng/ml) was 26.3±12.0 in the CG and 19.4±6.8 in the RD group ($p<0.0001$). Moreover, CG had lower percentage of individuals with 25OHD deficiency compared to RD (29.9% vs 53.2%). The femoral neck BMD was significantly lower in postmenopausal RD women compared to CG. 25OHD levels significantly correlated with ESR and CRP as inflammatory markers. Age, BMI, presence of RD, and CRP were significantly and negatively associated with 25OHD levels through linear regression analysis. According to univariate logistic regression analysis for 25OHD deficiency (<20 ng/ml), a significant and negative association with BMI, presence of RD, ESR and CRP were found.

Conclusion

Patients with RD had lower 25OHD levels than controls and the presence of a RD increases by 2.66 the risk of vitamin D deficiency. In addition, 25OHD has a negative correlation with ESR and CRP as inflammatory markers.

Keywords: 25-hydroxyvitamin D, rheumatologic diseases, inflammatory markers, C-reactive protein, erythrocyte sedimentation rate.

E-mail: lorenabrance@conicet.gov.ar

Resumen

ASOCIACIÓN NEGATIVA ENTRE 25-HIDROXI VITAMINA D Y LOS MARCADORES INFLAMATORIOS EN ENFERMEDADES REUMATOLÓGICAS

Objetivo

El objetivo principal de este estudio fue evaluar los niveles séricos de 25-hidroxivitamina D (25OHD) y su asociación con marcadores inflamatorios en enfermedades reumatológicas.

Materiales y métodos

Se realizó un estudio transversal en 154 mujeres con enfermedades reumatológicas (artritis reumatoide, espondiloartritis y otras enfermedades del tejido conectivo) y 112 individuos sanos como grupo control (GC).

Resultados

No se encontraron diferencias en el calcio sérico y urinario, el fosfato sérico y la desoxipiridinolina urinaria entre el GC y los sujetos con enfermedades reumatológicas. El grupo de pacientes con enfermedades reumatológicas tenía 25OHD más bajo y PTH más alto en comparación con el GC. Asimismo, el grupo de individuos con enfermedades reumatológicas tenía proteína C reactiva (PCR) y velocidad de eritrosedimentación (VES) más altas en comparación con el GC. El nivel de 25OHD (ng/ml) fue 26,3±12,0 en el GC y 19,4±6,8 en el grupo con enfermedades reumatológicas (p<0,0001). Además, el GC presentó un porcentaje menor de deficiencia de 25OHD en comparación con el grupo con enfermedades reumatológicas (29,9% vs 53,2%). La DMO del cuello femoral fue significativamente menor en las mujeres posmenopáusicas con enfermedades reumatológicas en comparación con el GC. La 25OHD correlacionó significativamente con la VES y la PCR como marcadores inflamatorios. El análisis de regresión lineal mostró que la edad, el IMC, la presencia de una enfermedad reumatológica y la PCR se asociaron significativa y negativamente con los niveles de 25OHD. Mientras que el análisis de regresión logística univariada mostró que la deficiencia de 25OHD (<20 ng/ml), se asoció significativa y negativamente con el IMC, la presencia de una enfermedad reumatológica, la VES y los niveles de PCR.

Conclusiones

Los pacientes con enfermedades reumatológicas tenían niveles de 25OHD más bajos que los controles y la presencia de una enfermedad reumatológica aumenta en 2.66 el riesgo de deficiencia de vitamina D. Además, la 25OHD mostró correlación negativa con la VES y la PCR como marcadores inflamatorios.

Palabras claves: *25-hidroxi vitamina D, enfermedades reumatológicas, marcadores inflamatorios, proteína C-reactiva, velocidad de eritrosedimentación.*

Introduction

Hypovitaminosis D has been widely associated with acute and chronic health disorders. Previous evidence indicates an association between vitamin D deficiency and an increased incidence of autoimmune diseases. The presence of the vitamin D receptor (VDR) in cells of the immune system suggests that vitamin D also has effects on the modulation of both innate and adaptive immunity. Dendritic cells, monocytes, and macrophages express 1α-hydroxylase, which converts 25-hydroxyvitamin D (25OHD) to its active form 1,25 dihydroxyvitamin D [1,25$(OH)_2$D or calcitriol] with autocrine and paracrine effects.

Moreover, 25OHD levels negatively correlate with rheumatoid arthritis (RA) activity. In Chinese RA patients without glucocorticoid treatment, low 25OHD levels correlate with low

bone mineral density (BMD) and high disease activity. Previously, we found low 25OHD levels associated with moderate-high disease activity suggesting the importance of optimal 25OHD levels in RA patients. Furthermore, after 1 year of vitamin D treatment, 25OHD levels increased while the disease activity score (DAS-28) decreased. Vitamin D deficiency is highly prevalent in patients with systemic lupus erythematosus (SLE) and severe deficiency increases the risk for moderate to severe disease activity, but not for organ damage in these patients. In a large cross-sectional study of SLE patients, 25OHD levels negatively correlated with disease activity.[13] In addition, higher 25OHD levels were associated with a decreased risk of ankylosing spondylitis and 25OHD levels showed an inverse relationship with disease activity. Vitamin D deficiency has also been associated with other autoimmune diseases such as systemic sclerosis, diabetes mellitus, inflammatory bowel disease, mixed connective tissue disease, and autoimmune thyroid disease.

As summarized in a systematic review, eight longitudinal studies reported 25OHD outcomes during acute inflammatory response (4 due to elective surgery, 1 to intravenous bisphosphonate administration, and to 3 acute illness). In most studies, 25OHD levels had a rapid significant decrease during the acute-phase response, while an opposite change in serum C-reactive protein (CRP) was observed. In addition, in large cross-sectional studies of asymptomatic adults of United States (n=15167) and England (n=5870) an inverse relationship between 25OHD and CRP was found.[13] On the other hand, 25OHD levels were not associated with subclinical vascular disease or CRP in the Old Order Amish population and no correlation was found between 25OHD and plasma fibrinogen levels as inflammatory marker.[14] Moreover, a negative relationship between serum 25OHD and CRP but not with erythrocyte sedimentation rate (ESR) was observed in RA patients.[15]

Because rheumatologic disease (RD) activity has been associated with low 25OHD levels, we hypothesized that 25OHD could be negatively associated with the acute-phase response. Therefore, this study aimed to evaluate serum 25OHD and its association with inflammatory markers in women with rheumatologic diseases.

Patients and methods

A cross-sectional study in 266 women from Rosario (32º52'18"S) and Buenos Aires (34°36'30"S) cities, Argentina, was carried out.

We included 154 patients with RD according to international criteria: 83 with a diagnosis of rheumatoid arthritis (RA), 18 with spondyloarthropathies (SA) and 53 with connective tissue diseases (CTD) as systemic lupus erythematosus, vasculitis, systemic sclerosis, undifferentiated disease, and overlap syndrome. To be included, patients had to be older than 18 years, and have a RD diagnosed at least 1 year before. Patients were excluded if they had pregnancy, intestinal malabsorption, chronic liver or kidney disease, and history of neoplasia or had taken drugs that affect bone metabolism, including bisphosphonates, calcium, and vitamin D supplementation in the last 12 months (except glucocorticoid treatment in RD). As control group (CG), 112 healthy individuals from general population matched by age, sex, and body mass index (BMI) were included.

Serum calcium (mg/dl) and phosphate (mg/dl), urinary calcium (mg/24-h) and serum alkaline phosphatase (IU/l) were assessed by standard techniques. Parathyroid hormone (PTH, pg/ml) was measured by immunoassay (Cobas, Roche Basel, Switzerland), urinary deoxypyridinoline (DpD, nM/mM creatine), C-reactive protein (CRP, mg/l) by an immunoturbidimetric assay, and erythrocyte sedimentation rate (ESR, mm/h) by the Westergreen method. Total 25OHD levels (D2+D3) were measured

using a chemiluminescence assay (ADVIA Centaur Vitamin D Total Assay - Siemens). 25OHD severe deficiency was defined as 25OHD levels <10 ng/ml, deficiency as 25OHD levels between 10-20 ng/ml, insufficiency as 25OHD levels between 20-30 ng/ml (50-75 nmol/liter), and 25OHD levels >30 ng/ml were considered as optimal. When 25OHD was analyzed as a categorical variable, 25OHD deficiency (≤ 20 ng/ml) was used as cut-off.

Weight (kg) and height (m) as anthropometric parameters were recorded to calculate body mass index (BMI, kg/m^2). BMD (g/cm^2) was measured by dual-energy X-ray absorptiometry (DXA) with GE Lunar Prodigy (GE Lunar, Madison, WI, USA) at the lumbar spine (L1-L4) and femoral neck. The coefficient of variation was less than 1%. According to the BMD, osteoporosis was diagnosed when the T-score was –2.5 SD or lower and osteopenia when the T-score was between -1.0 and –2.5 SD in postmenopausal (postM) women. In premenopausal (preM) women, low bone mass for age was defined when the Z-score was –2.0 SD or lower.[7] Thoracic and lumbar spine lateral X-ray films were used to determine the presence of vertebral fractures. Non-vertebral fractures data were obtained from medical records.

Disease activity or functional indices were used to classified as low, moderate, or severe according to appropriate scores: DAS-28 and HAQ-I in RA patients, SLEDAI in SLE patients and BASFI, BASDAI, HAQ in SA patients.

The study was approved by the Ethics Committee of the School of Medical Sciences, Rosario National University (Argentina) and conducted in compliance with the Declaration of Helsinki. All patients gave written informed consent to be included and each participant was identified by a number in order to keep their identity confidential.

Statistical analysis

Categorical variables were expressed as number (percentages) and continuous variables as mean±standard deviation (SD) for normally distributed data or media (25th-75th percentiles) for skewed data as evaluated by the Kolmogorov-Smirnov test. Differences between CG and RD patients were analyzed using the Student t-test or Mann-Whitney test as appropriate. When more than two groups were analyzed one-way ANOVA or Kruskal-Wallis test were used when appropriate. Contingency tables were evaluated with χ^2 test. Correlations were performed with Pearson or Spearman's correlation test. Univariate logistic regression analysis for 25OHD deficiency (<20 ng/ml) was performed with the *software* R 3.3.3. Differences were considered significant if $p<0.05$.

Results

A total of 266 subjects (154 with RD and 112 CG) were included in the study. The baseline characteristics are shown in Table 1. No differences in age, BMI, percentage of pre- and postmenopausal women (CG= 22.4/77.6%, RD= 32.6/67.4%), serum and urine calcium, serum phosphate and urinary deoxypyridinoline were found (Table 1). In addition, there were no significant differences among controls and individual RD subgroups (data not shown). No significant differences in disease duration were observed between the RD subgroups (RA=8.9±8.6 y, SA=4.7±7.1 y, CTD=8.0±9.8 y).

RD group had lower 25OHD and higher PTH, alkaline phosphatase, CRP and ESR compared to CG (Table 1). There were no differences in hematocrit, hemoglobin, blood glucose, urea, aspartate transaminase, alanine transaminase, and lipid profile. Moreover, no differences among RD subgroups were observed (data not shown).

There were no significant differences in lumbar spine BMD in preM or postM RD patients compared to controls (Table 2).

Table 1. Main characteristics of the study population.

	Control (n=112)	**RD** (n=154)	**p**
Age (years)	56.0±13.4	53.2±13.8	ns
BMI (kg/m^2)	25.6±4.7	26.7±4.8	ns
Disease duration (years)	-	8.3±9.0	-
Glucocorticoid therapy (mg prednisone or equivalent)	-	5.0 (4.0-7.5)	-
Serum calcium (mg/dl, range: 8.5-10.5)	9.3±0.**5**	9.2±0.6	ns
Urine calcium (mg/24 h, range: 100-250)	145.9±73.0	166.5±76.1	ns
Serum phosphate (mg/dl, range: 2.5-4.5)	3.5±0.6	3.4±0.6	ns
25OHD (ng/ml)	26.3±12.0	19.4±6.8	**<0.0001**
PTH (pg/ml, range: 15-65)	39.6±14.5	48.1±17.5	**0.0170**
AP (UI/L, range: 90-270)	106.8±58.2	153.6±76.9	**<0.0001**
Urinary deoxipyridinoline (nM/mM creatine)	8.5±8.4	7.9±2.3	ns
CRP (mg/dl)	0.0 (0.0-0.2)	2.2 (0.5-6.0)	**<0.0001**
ESR (mm/h)	5.0 (5.0-6.0)	25.0 (10.5-35.0)	**<0.0001**

Mean±standard deviation (SD) for normally distributed data or media (25th-75th percentiles) for skewed data. Abbreviations: BMI: body mass index, GC: glucocorticoids, AP: alkaline phosphatase *ESR: eritrosedimentation rate. CRP: C-reactive protein.*

However, femoral neck BMD was significantly lower in postM RD patients (0.761±0.152 g/cm^2; T-score -1.8±1.2) compared to postM control subjects (0.804±0.123 g/cm^2; T-score -1.2±0.9) (Table 2, p<0.05). Despite a higher percentage of vertebral and non-vertebral fractures in RD patients compared to controls, the difference between the groups did not reach significance.

Serum 25-hydroxyvitamin D in rheumatologic diseases according to age and BMI

The overall mean level of 25OHD was 26.3±12.0 ng/ml in the CG and 19.4±6.8 ng/ml in the RD group (p<0.0001). In addition, each RD subgroup showed significant differences compared to CG (Figure 1, p<0.0001). Moreover, the CG had lower percentage of 25OHD deficiency (≤20 ng/ml) compared to RD group (29.9% vs 53.2%) (χ^2 test, p<0.0001).

A negative correlation between 25OHD and age was observed in CG (r= -0.27; p=0.0044). However, this correlation was not observed in RD (p>0.05). Regardless the age, RD patients had significantly lower 25OHD levels compared to the CG (Figure 2).

A negative correlation between 25OHD and BMI were observed in CG, RD and the whole group (r= -0.22; p=0.0010). Furthermore, significantly lower 25OHD levels between CG and RD were found in the group of patients with BMI<25 and >30, without differences in subjects with BMI between 25 and 30.

Table 2. Bone mass and prevalence of vertebral and non-vertebral fractures.

	Control (n=112)	RD (n=154)	p
PreM/PostM (%)	22.4/77.6	32.6/67.4	ns
PreM lumbar spine			
BMD (g/cm^2)	1.095±0.159	1.114±0.098	ns
Z-score	-0.3±1.0	0.3±1.0	ns
PostM lumbar spine			
BMD (g/cm^2)	0.978±0.148	0.935±0.165	ns
T-score	-1.6±1.1	-1.8±1.3	ns
PostM femoral neck			
BMD (g/cm^2)	0.804±0.123	0.761±0.152	**0.0168**
T-score	-1.2±0.9	-1.8±1.2	**0.0056**
Vertebral Fracture (%)	3.2	6.6	ns
Non-vertebral Fracture (%)	6.2	10.0	ns

Abbreviations: PreM: premenopausal; PostM: postmenopausal.

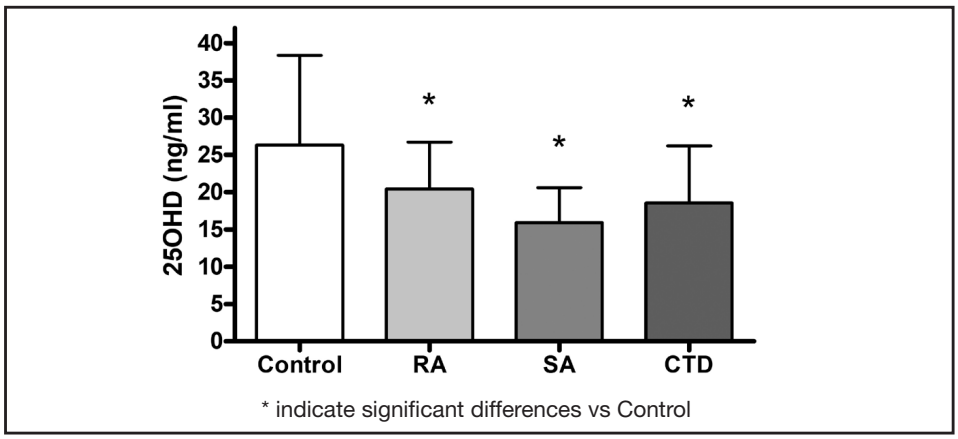

Figure 1. 25OHD in RD subgroups compared to controls.

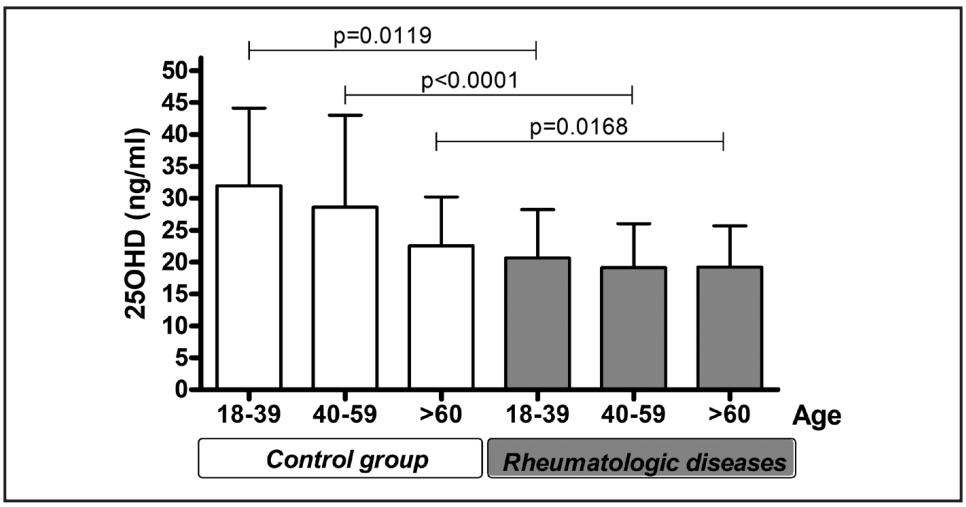

Figure 2. 25OHD according to age in RD and CG.

Serum 25-Hydroxyvitamin D and inflammatory markers

RD patients had higher ESR and CRP compared to controls. Interestingly, 25OHD significantly correlated with ESR (r= -0.37; p<0.0001) and CRP (r= -0.35; p<0.0001). Age, BMI, presence of RD and CRP were significantly and negatively associated with 25OHD levels according to linear regression analysis.

Univariate logistic regression analysis for 25OHD deficiency (<20 ng/ml) revealed a significant and negative association within the following variables: BMI, presence of RD, ESR and CRP (Table 3). Furthermore, the presence of a RD increased by 2.66 the risk of vitamin D deficiency.

Discussion

Many prospective studies have shown associations between 25OHD deficiency and a wide range of acute and chronic health disorders. However, the randomized trials have not confirmed that rising of 25OHD concentrations can modify the occurrence or clinical course of these disorders. Therefore, 25OHD deficiency could be the result of inflammatory processes involved in the occurrence and progression of disease. Despite the fact that hypovitaminosis D was found in both CG and RD groups, RD and each RD subgroup had lower levels compared to controls. Hypovitaminosis D is also highly prevalent among autoimmune rheumatologic diseases population in China. Consistent with this study, we found a higher percentage of 25OHD deficiency (≤20 ng/ml) in the RD group (53.2%) compared to controls (29.9%). Furthermore, all RD subgroups showed lower 25OHD levels than CG. Several mechanisms could be responsible for a decrease in 25OHD levels such as decreased vitamin D carrier proteins and an increased conversion of 25OHD to 1,25-dihydroxyvitamin D.[12]

Moreover, although circulating PTH values are in the normal range in all groups, RD patients had significantly higher values compared to the glucocorticoid group. The vitamin D deficiency and the increased PTH in RD would indicate secondary hyperparathyroidism, which could explain -at least in part- the negative effects on bone, in particular in the femoral neck. There were no differences in lumbar spine BMD between RD and CG. These findings are consistent with a previous study, which found an association

Table 3. Odd ratio (OR) for 25OHD deficiency (<20 ng/ml). Univariate logistic regression.

	OR	IC95%	p
Age	1.009	0.991-1.028	ns
BMI	1.009	1.005-1.014	**<0.0001**
Presence of RD (yes)	2.663	1.578-4.563	**0.0002**
ESR	1.042	1.023-1.066	**<0.0001**
CRP	1.040	1.020-1.063	**0.0001**
Disease activity (moderate)	1.457	0.611-3.517	ns
Disease activity (severe)	1.187	0.418-3.391	ns

Abbreviations: BMI: body mass index, ESR: eritrosedimentation rate. CRP: C-reactive protein.

between moderate RA activity and low BMD in the femoral neck rather than in the spine and with a previous study in RA patients reported by us.[7] Therefore, femoral neck BMD should be explored regardless of age in patients with autoimmune RD. In addition, bone could be affected by other factors in RD such as disease activity, immobilization, and glucocorticoid treatment which increase the risk of osteoporotic fractures, a major complication in patients with RD.[1] Previous studies have shown higher prevalence of vertebral and non-vertebral fractures in RD patients.[1] Here we did not find significant differences in fractures, although a trend to higher percentage was observed in RD patients (Table 2).

A negative correlation between 25OHD and BMI was also observed. A negative correlation between 25OHD and age in the CG without correlation in RD patients was found indicating that other factors would be affecting vitamin D levels. Nevertheless, lower 25OHD levels were found in RD in all evaluated age ranges (Figure 2). Aging is associated with vitamin D deficiency possibly due lower sun exposure and physical activity, loss of appetite, and endogenous vitamin D synthesis. SLE patients have lower sun exposure and RA and SA patients have lower physical activity due to the involvement of their joints, bones, and muscles. Furthermore, local and systemic inflammation are also related to low 25OHD levels 1.

All autoimmune RD have different expression of proinflammatory cytokines and mediates systemic effects that promote acute-phase responses. ESR and CRP are commonly measured as inflammation markers. In this study, the RD group showed significantly higher values of ESR and CRP compared to controls and 25OHD significantly correlated with ESR and CRP. Moreover, according to the linear regression analysis, CRP was significantly and negatively associated with 25OHD levels. In the univariate logistic regression analysis for 25OHD deficiency (<20 ng/ml) a significant association with ESR and CRP were found. These findings are consistent with a previous study in RA patients and would suggest that 25OHD levels are inversely associated with inflammatory markers in patients with RD. In a meta-analysis that included a total of 24 reports involving 3489 patients, lower 25OHD levels were found in RA patients compared to healthy controls. In addition, a negative relationship between 25OHD levels and DAS28 and 25OHD levels and CRP were observed.[5] However, the relationship between 25OHD and ESR was not conclusive. This may be partly because CRP is a more direct measure of inflammation, more sensitive to short-term changes than ESR5. Consistent with our results, a previous study in RA patients, in which it was described that 25OHD was also negatively associated with serum levels of IL-17 and IL-23 as inflammatory cytokines.

In a systematic review about 25OHD levels and its association with inflammatory diseases, higher CRP and lower 25OHD levels were found in different clinical situations as knee-hip arthroplasty, acute pancreatitis, and orthopedic surgery. In addition, in asymptomatic adults in the United States (n=15167), a negative relationship between vitamin D and CRP was found, particularly with low 25OHD levels (<21 ng/ml)[13] consistent with our data in which a mean 19.4 ng/ml was found in RD patients.

Further, in a recent study, associations between inflammatory markers were investigated in treatment-naïve patients with RD. They concluded that ESR, CRP, and white blood cell count are not always elevated and inflammatory markers are not specific for disease diagnosis.

Some limitations of this study as cross-sectional study and small sample in certain RD subgroups should be pointed out. Longitudinal studies would be necessary to confirm the association between 25OHD and inflammatory markers.

Conclusion

In conclusion, patients with RD have lower 25OHD levels than controls and the presence of a RD increases by 2.66 the risk of vitamin D deficiency. In addition, 25OHD levels have a negative correlation with ESR and CRP as inflammatory markers.

The measurement of vitamin D levels in patients with autoimmune disorders would be useful to reach optimal 25OHD levels and thus improve the effectiveness of vitamin D, not only on bone and muscle but also on inflammatory markers.

Declaration of interest. All authors have no conflicts of interest.

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