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Original article

Associations between serum 25-hydroxyvitamin D and disease activity, inflammatory cytokines and bone loss in patients with rheumatoid arthritis

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Abstract

Objective. The aim of this study was to describe the associations between serum levels of 25-hydroxyvitamin D [25(OH)D] and disease activity, inflammatory cytokines and bone loss/erosions in patients with RA.

Methods. The study included 130 patients with RA and 80 healthy controls. Serum 25(OH)D, IL-17 and IL-23 levels were detected by ELISA. Radiographic bone erosion was assessed using the van der Heijde modified Sharp score and BMD was measured using DXA.

Results. There were no significant differences in age, gender and BMI between the RA and control groups. Serum level of 25(OH)D was markedly lower in the RA group than in the control group [43.12 nmol/l (S.D. 15.59) *vs* 57.93 (15.95), $P < 0.01$]. In RA patients, 25(OH)D levels were significantly and negatively associated with clinical parameters of disease activity including swollen joint count, tender joint count, joint pain degree, morning stiffness time and HAQ score and laboratory measures including platelets and ESR after adjustment for gender, age and BMI. They were also negatively associated with serum levels of IL-17 and IL-23. While 25(OH)D levels were not associated with radiographic bone erosions of RA, they were significantly lower in those with osteopenia and osteoporosis than in those with normal BMD ($P < 0.01$).

Conclusion. 25(OH)D levels were reduced in patients with RA and were negatively associated with disease activity, IL-17/IL-23 and bone loss in RA. These suggest that vitamin D deficiency may play a role in the aetiology of RA.

Key words: arthritis, rheumatoid, 25-hydroxyvitamin D, disease activity, IL-17, IL-23.

CLINICAL SCIENCE

Introduction

RA is a chronic inflammatory autoimmune disease that predominantly involves synovial joints and affects up to 1% of adults worldwide, with 5–50 per 100 000 new cases annually. Despite this relatively high prevalence rate, the aetiology and pathogenesis of RA remain obscure and a number of factors have been implicated in its pathogenesis. One of the most recent factors found to be associated with autoimmunity is vitamin D deficiency.

Vitamin D is a secosteroid hormone that is produced in the skin from 7-dehydrocholesterol under the influence of sunlight as well as intake from the diet. In the liver, vitamin D is converted to 25-hydroxyvitamin D [25(OH)D], which is the specific vitamin D metabolite that is measured in serum to determine a person's vitamin D status [1]. In the kidneys and extrarenal tissues, 25(OH)D is converted into calcitriol, i.e. $1,25(OH)_2D_3$, the biologically active form of vitamin D [2], which mediates its biological effects by binding to the vitamin D receptor. Circulating 25(OH)D

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concentrations decreased with the evolution of the systemic inflammatory response [3]. The immunoregulatory effects of $1,25(OH)_2D_3$ are a result of its action on regulating immune cells, including macrophages and lymphocytes, to suppress the production of IL-17, IL-23 and TNF-α, and to augment the expression of IL-4 and IL-10 [4, 5]. Therefore it is plausible to hypothesize that vitamin D deficiency may play a role in immunological dysfunction.

The IL-23–IL-17 axis is a significant mediator of inflammation [6]. Studies have reported that increased IL-17 and IL-23 are associated with increased disease activity in patients with RA [7, 8], but there is little evidence to show whether vitamin D status is associated with serum levels of IL-17 and IL-23 in RA patients. Vitamin D levels might influence RA disease activity, as assessed by the 28-joint DAS (DAS28) [9], however, some studies have reported no significant associations between vitamin D insufficiency and joint pain or disease activity [10]. These inconsistencies may be due to differences in factors such as study population, design, sample size and analytical methods.

RA is characterized by bone erosions in the articular facet and subarticular facet, i.e. osteoporosis (OP). Inflammatory factors have been known to accelerate the progression of bone erosions, and both focal inflammation and glucocorticoid therapy can induce OP in RA patients. Vitamin D can directly regulate calcium and phosphorus metabolism, promoting the healthy mineralization, growth and remodelling of bone. Low 25(OH)D levels in RA [11, 12] may be associated with bone erosion and OP, however, there are few data to support this. The aim of the study was to describe the associations between serum levels of 25(OH)D and disease activity, inflammatory cytokines and bone loss/erosions in patients with RA.

Materials and methods

Patients and controls

The study population included 130 patients with RA [95 women and 35 men, mean age 54 years (S.D. 14), age range 19–83 years, BMI 21.91 kg/m^2 (S.D. 3.07)] who attended the clinic at the Department of Rheumatology and Immunology, First Affiliated Hospital of Anhui Medical University in China (latitude 32°). RA was diagnosed using the 1987 revised ACR criteria [13]. Patients with other inflammatory diseases, thyroid or parathyroid gland diseases, other endocrine disorders or serious liver or kidney diseases were excluded. Patients were also excluded if they had concomitant use of vitamin D supplements. Simultaneously we randomly recruited 80 healthy subjects from the local community, matched by age (±2 years) and sex to the patients [57 women and 23 men, age range 24–78 years with a mean age of 54 years (S.D. 13), BMI 21.78 kg/m^2 (S.D. 2.17)]. To avoid the influence caused by seasonal variations in vitamin D status throughout the year, the participants were enrolled between October 2011 and April 2012.

All RA patients were classified into three groups according to their DAS28: low (DAS28 $<$ 3.2), moderate (DAS28 3.2–5.1) and severe (DAS28 $>$ 5.1). The DAS28 was calculated using ESR and the Nijmegen formula: DAS28(ESR) = 0.56*(TJC28)$^{1/2}$ + 0.28*(SJC28)$^{1/2}$ + 0.014*GH + 0.70*ln(ESR). Each patient's age, sex, height, weight, duration of disease, morning stiffness time, tender joint count (TJC), swollen joint count (SJC) and HAQ score were assessed; ESR, CRP, RF, anti-CCP and routine biochemistry were measured; and the Sharp scores for both hands were determined. This study was performed according to the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the First Affiliated Hospital of Anhui Medical University. Each participant provided written informed consent.

Vitamin D, IL-17 and IL-23 measurement

All serum 25(OH)D levels in patients and controls were detected by ELISA using reagents supplied by Immunodiagnostic Systems (IDS; Boldon, Tyne & Wear, UK) and the quantitative measures of IL-17 and IL-23 were performed by ELISA using reagents supplied by Yuanye Biological Technology (Shanghai, China) in a single batch of baseline samples stored at −80°C. The ELISA tests were performed according to the manufacturer's instructions. The optical density was measured at 450 nm using an automatic ELISA reader (Sunrise; Tecan, Männedorf, Switzerland).

Patients were classified based on their 25(OH)D levels into whether they were deficient [$<$50 nmol/l ($<$20 ng/ml)], insufficient [50–75 nmol/l (20–30 ng/ml)] or within the recommended range [$>$75 nmol/l ($>$30 ng/ml)] [14, 15].

BMD measurement

BMD of the lumbar spine (L2–L4) and proximal femur, including the femoral neck, Wards triangle and greater trochanter, were measured by DXA with a Lunar Prodigy (GE Healthcare, Shanghai, China). BMD was automatically calculated from the bone area (cm^2) and bone mineral content (g) and expressed absolutely (g/cm^2). OP was diagnosed using *T* scores calculated from gender-matched BMD data from young adults in China [16]. Patients were classified into those with normal BMD, osteopenia and OP based on *T* scores using the World Health Organization classification [17]. BMD was measured in 106 patients.

Bone erosion assessment

X-rays of the hands and wrists were available for 106 RA patients. The presence or absence of radiographic bone erosions was assessed. In addition, the van der Heijde modified Sharp score, including 17 areas read for erosions and 18 areas read for joint space narrowing, were determined using standardized methods, as previously described [18, 19].

Statistical analyses

Statistical analyses were performed using SPSS software (version 19.0; IBM, Armonk, NY, USA). Data are presented as mean (S.D.) or median [interquartile range (IQR)]. IL-17

and IL-23 levels were not normally distributed and were log transformed for the analyses. The subgroup differences were assessed by two-tailed independent samples *t* tests, analysis of variance (ANOVA) or chi-square tests as appropriate. Univariable and multivariable linear regression models were used to determine the associations between 25(OH)D and outcome measures (disease activity, inflammatory markers, etc.) before and after adjustment for age, sex and BMI. A *P*-value <0.05 was considered statistically significant.

Results

One hundred and thirty RA patients (73.1% females) with a mean disease duration of 6 years (range 2 months–40 years) and 80 normal subjects were studied. There were no statistically significant differences in terms of the main characteristics between the patient and control groups. Characteristics of the participants are presented in Table 1. In multivariable analyses, while sex, weight, height and BMI were not significantly associated with serum 25(OH)D levels, there was a negative association between age and serum 25(OH)D levels in the control group ($\beta = -0.26$, 95% CI -0.23, -0.02) and all participants ($\beta = -0.19$, 95% CI -0.17, -0.03).

Patients with RA showed a significantly lower serum level of 25(OH)D compared with controls ($P < 0.001$; Fig. 1A). Vitamin D sufficiency was found in two patients (1.5%), insufficiency in 43 patients (33.1%) and deficiency in 85 patients (65.4%), while vitamin D sufficiency was reported in 10 healthy matched controls (12.5%), insufficiency in 44 (55%) controls and deficiency in 26 (32.5%) controls. RA patients had a higher prevalence of 25(OH)D insufficiency/deficiency (98.5%) than healthy controls (87.5%) ($\chi^2 = 26.291$, $P < 0.001$).

Results for the associations between clinical and laboratory variables and serum 25(OH)D levels are shown in Table 2. Serum 25(OH)D levels were significantly associated with SJC, TJC, joint pain score, morning stiffness time, HAQ score, DAS28, platelets, ESR, CRP, IL-17 and IL-23 and all these associations (except with CRP) remained statistically significant after adjustment for sex, age and BMI. The associations between serum 25(OH)D levels and disease activities (SJC, TJC, joint pain score, morning stiffness time, HAQ score and DAS28) decreased in magnitude by 14–24% but remained significant after further adjustment for IL-17 or IL-23 (data not shown). In contrast, 25(OH)D levels were not significantly associated with RF and anti-CCP antibody in the multivariable analysis.

Thirty-two RA patients had low (group I), 33 had moderate (group II) and 65 had severe (group III) disease activity. Serum levels of 25(OH)D were significantly higher in group I [54.70 nmol/l (S.D. 10.11)] than in group II [41.49 nmol/l (S.D. 16.07)] and group III [38.25 nmol/l (S.D. 14.78)] (Fig. 2A).

In RA patients the concentrations of IL-17 and IL-23 were significantly higher than in controls (both $P < 0.001$, non-parameter tests; Fig. 1B and C). The concentrations of IL-17 (Fig. 2B) and IL-23 (Fig. 2C) were positively and

Table 1 Characteristics of patients with RA and controls

Variable	RA ($n = 130$)	Controls ($n = 80$)	*P*-value
Age, mean (S.D.), years	54 (14)	54 (13)	0.818
Weight, mean (S.D.), kg	58 (10)	58 (9)	0.992
Height, mean (S.D.), m	1.62 (0.07)	1.63 (0.07)	0.623
BMI, mean (S.D.), kg/m^2	21.91 (3.07)	21.78 (2.17)	0.717
Female:male ratio	95:35	57:23	0.774
Disease duration, median (IQR), years	6 (2, 13)		
TJC, median (IQR)	9 (3, 17)		
SJC, median (IQR)	4 (2, 11)		
Morning stiffness time, median (IQR), min	30 (10, 60)		
Degree of pain[a], median (IQR)	50 (40, 67)		
HAQ score, mean (S.D.)	1.56 (0.89)		
DAS28 score, mean (S.D.)	4.95 (2.11)		
Platelets ($\times 10^9$/l), median (IQR)	251 (190, 354)		
ESR, median (IQR), mm/h	57 (27, 92)		
CRP, median (IQR), mg/l	27.00 (10.21, 51.51)		
RF, median (IQR), IU/ml	96 (44, 163)		
Anti-CCP antibody, median (IQR), RU/ml	457 (119, 1211)		
25(OH)D, mean (S.D.), nmol/l	43.12 (15.59)	57.93 (15.95)	
IL-17, median (IQR), pg/ml	22.45 (13.21, 28.15)	9.22 (5.24, 14.13)	
IL-23, median (IQR), pg/ml	152.56 (99.90, 204.89)	49.71 (35.92, 77.06)	
van der Heidje erosion score, median (IQR)	13 (4, 35)		
Joint space narrowing score, median (IQR)	10 (2, 34)		
Sharp score, median (IQR)	21 (7, 75)		

[a]A visual analogue scale was adopted to assess degree of joint pain. IQR: interquartile range; TJC: tender joint count; SJC: swollen joint count; DAS28: 28-joint DAS.

FIG. 1 Serum levels of (A) 25-hydroxyvitamin D (nmol/l), (B) IL-17 (pg/ml) and (C) IL-23 (pg/ml) in the RA and control groups

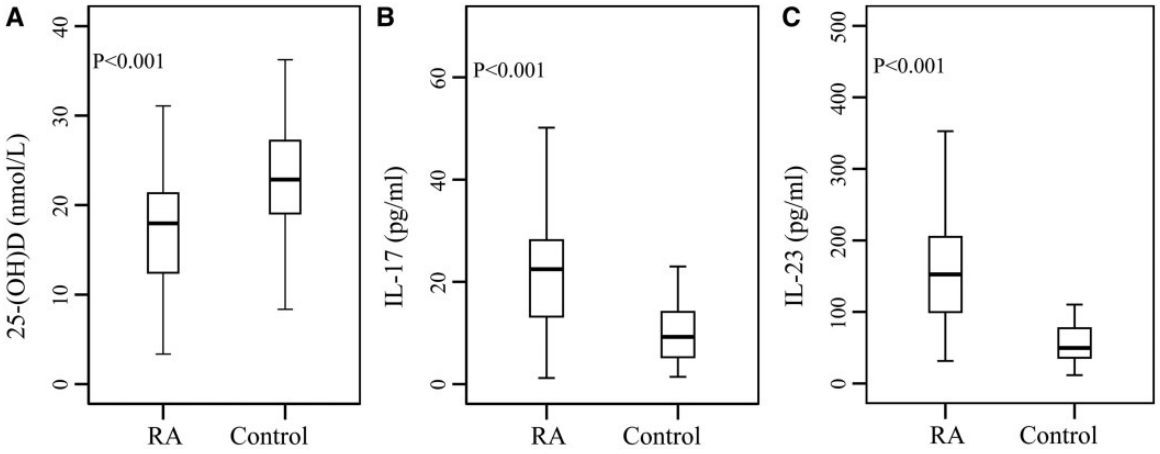


TABLE 2 Associations between clinical and laboratory variables (dependent variables) and serum 25(OH)D (nmol/l; independent variable) in patients with RA

Dependent variable	Univariable β (95% CI)	Multivariable[a] β (95% CI)
SJC	**−0.24 (−0.17, −0.03)**	**−0.28 (−0.18, −0.04)**
TJC	**−0.31 (−0.28, −0.08)**	**−0.32 (−0.30, −0.09)**
Morning stiffness time	**−0.37 (−3.05, −1.19)**	**−0.41 (−3.31, −1.37)**
Degree of pain[b]	**−0.34 (−0.85, −0.29)**	**−0.37 (−0.92, −0.34)**
HAQ score	**−0.38 (−0.03, −0.01)**	**−0.38 (−0.03, −0.01)**
DAS28 score	**−0.43 (−0.08, −0.04)**	**−0.46 (−0.08, −0.04)**
Platelets	**−0.24 (−2.84, −0.46)**	**−0.27 (−3.16, −0.67)**
ESR	**−0.37 (−1.35, −0.52)**	**−0.40 (−1.45, −0.58)**
CRP	**−0.18 (−0.88, −0.01)**	−0.17 (−0.89, 0.01)
RF	−0.02 (−1.01, 0.84)	−0.04 (−1.17, 0.78)
Anti-CCP antibody	+0.08 (−3.93, 9.60)	+0.07 (−4.52, 9.64)
IL-17	**−0.36 (−0.45, −0.20)**	**−0.36 (−0.46, −0.20)**
IL-23	**−0.34 (−2.92, −1.21)**	**−0.37 (−3.13, −1.38)**

[a]Adjusted for sex, age and BMI. [b]A visual analogue scale (VAS) was adopted to assess the degree of joint pain. Significant values in bold. 25(OH)D: 25-hydroxyvitamin D; SJC: swollen joint count; TJC: tender joint count; DAS28: 28-joint DAS.

significantly associated with DAS28 score. There was also a significantly positive correlation between IL-17 and IL-23 (Fig. 3A). Importantly, we found that IL-17 (Fig. 3B) and IL-23 (Fig. 3C) were significantly and negatively associated with 25(OH)D.

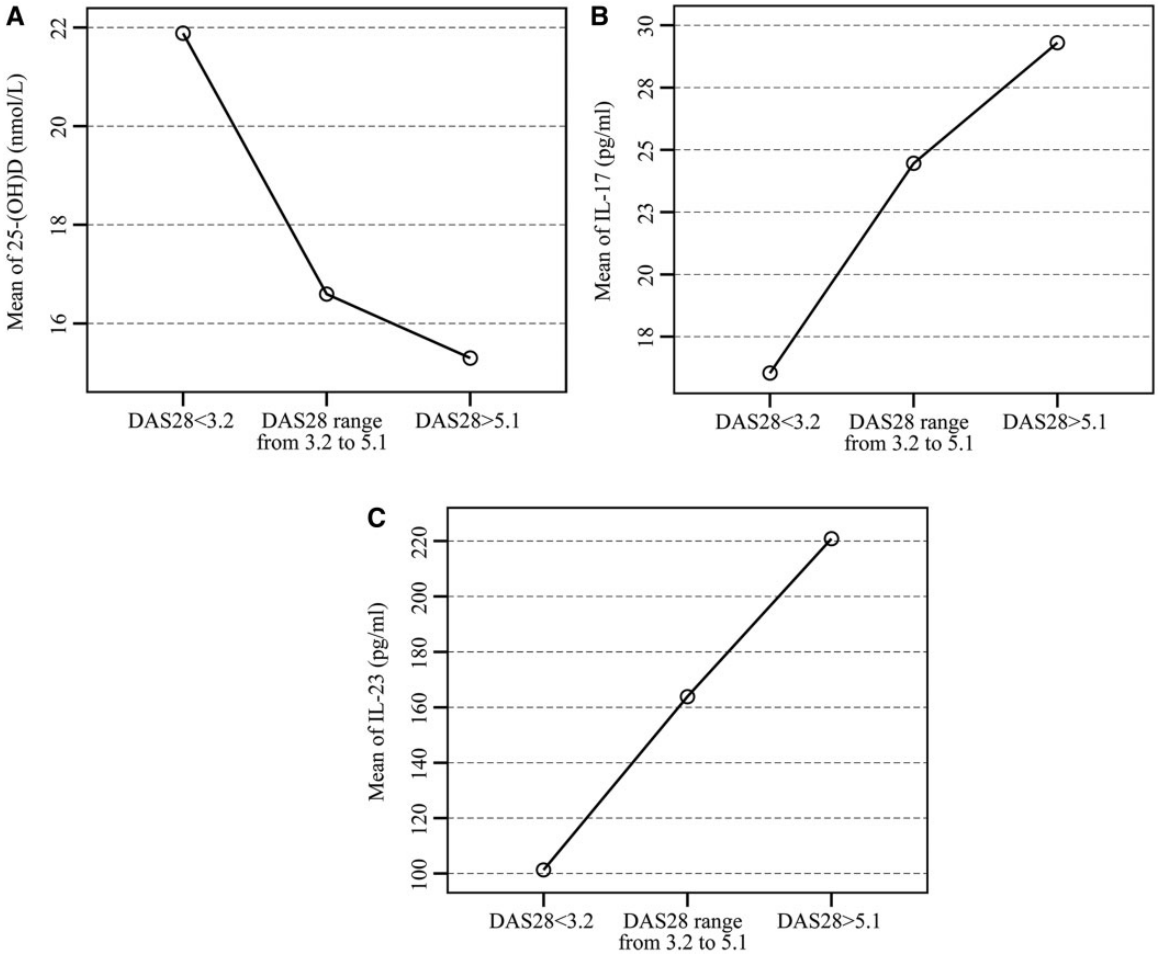
Using linear regression analyses, serum 25(OH)D levels were not associated with the van der Heijde modified Sharp score, including the van der Heidje erosion score and joint space narrowing score, in patients with RA (data not shown). Patients were divided into three groups based on the stage of radiographic erosion: 15 (14.2%) RA patients were stage I–II, 44 (41.5%) were stage III and 47 (44.3%) were stage IV. Differences in serum 25(OH)D levels among these three stages were not statistically significant (ANOVA; Table 3). Based on BMD assessments, we found that 42 (39.6%) RA patients had OP, 42 (39.6%) had osteopenia and 22 (20.8%) had normal BMD. Serum 25(OH)D levels were significantly higher in patients with normal BMD than in those with OP and osteopenia (all $P < 0.01$; Table 3). The associations remained significant after further adjustment for age, sex and BMI.

Discussion

In this study we utilized case–control and cross-sectional designs and found that serum levels of 25(OH)D were significantly lower in RA patients than in normal controls. In RA patients, lower levels of 25(OH)D were associated with increased disease activity, including SJC, TJC, joint pain degree, morning stiffness time and HAQ score. Serum levels of 25(OH)D were also negatively associated with DAS28 score, ESR, platelets, IL-17 and IL-23. Furthermore, patients with OP and osteopenia had significantly lower levels of 25(OH)D than those with normal BMD.

The immunoregulatory effects of vitamin D have been a hot topic. Vitamin D affects both the innate and adaptive immune responses, contributing to the immune tolerance of self-antigens. Vitamin D deficiency skews the immunological response towards loss of tolerance and may play an important role in autoimmune diseases including RA [20]. It has been reported that 25(OH)Dis associated with disease activity in RA [9,11, 12], and a meta-analysis showed that individuals in the group with the highest total vitamin D intake had a 24.2% lower risk of developing RA than those in the lowest group [21]; however, the mechanisms underlying this are unclear. We aimed to demonstrate whether vitamin D status is associated with

FIG. 2 Associations of 25-hydroxyvitamin D, IL-17 and IL-23 with disease activity based on the 28-joint DAS in patients with RA



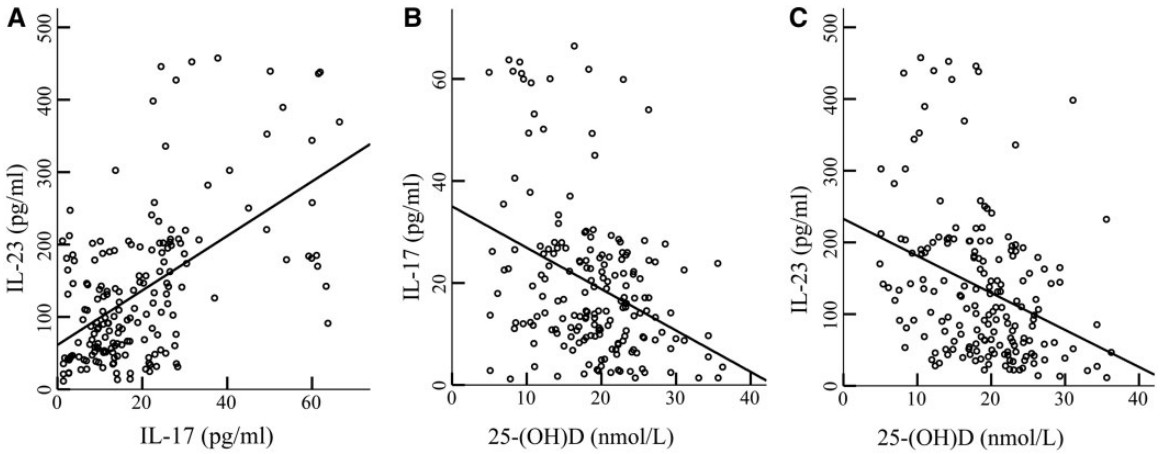
All $P < 0.01$.

clinical and laboratory parameters, including IL-17 and IL-23, in Chinese patients with RA, and this is the first study to address the associations between vitamin D status, IL-17 and IL-23 levels in RA.

Some previous studies utilized a case–control design to determine if 25(OH)D levels are different between RA patients and healthy controls, but these produced inconsistent results. While three studies reported that there were no significant differences in serum levels of 25(OH)D [9, 22, 23], two recent studies in Europe revealed that serum 25(OH)D levels in RA patients were significantly lower than in healthy controls [24, 25]. The reasons underlying these discrepancies are unclear but may be due to variations in factors such as study population, sample size and confounders such as age, BMI and time of year. Based on a small but very homogeneous sample of Chinese patients, we found that serum 25(OH)D levels were significantly lower in RA patients compared with those in healthy controls. The prevalence of vitamin D deficiency was significantly higher in RA patients (65.4% *vs* 32.5% in controls). Cases and controls were matched for age and sex, and BMI was similar between the two groups so the findings would not be confounded by these factors. 25(OH)D levels were measured in autumn to winter in both case and control groups, so our findings were also not affected by seasonal variations. Taken together, our results reveal that vitamin D deficiency may play a role in RA.

We further investigated the associations between serum 25(OH)D levels and disease activity in RA using a cross-sectional design. We found that serum concentrations of 25(OH)D were inversely and significantly associated with morning stiffness, TJC, SJC, ESR, platelet count, HAQ score and degree of joint pain. These associations were partly dependent on inflammatory cytokines IL-17 and IL-23. Consistent with our findings, Cutolo *et al.* [23, 26] reported a significant inverse association between 25(OH)D and DAS28 in patients with active RA. However, we did not find a significant association of 25(OH)D with RF and anti-CCP. Similarly, Feser *et al.* [27] reported that vitamin D levels were not associated with RA-related autoimmunity in subjects at risk of RA. The biological mechanisms underlying this remain unknown.

FIG. 3 Scatterplots for the associations between IL-17, IL-23 and 25-hydroxyvitamin D [25-(OH)D]



(**A**) IL-17 and IL-23: $\beta = 0.557$, $P < 0.001$; (**B**) 25(OH)D and IL-17: $\beta = -0.358$, $P < 0.001$; (**C**) 25(OH)D and IL-23: $\beta = -0.337$, $P < 0.001$.

TABLE 3 Association between 25(OH)D and stage of radiographic erosions and bone loss

	n	Serum 25(OH)D levels (nmol/l)	*P*-value[a]
X-ray erosions, mean (S.D.)			
Stage I–II	15	46.85 (10.94)	0.314
Stage III	44	39.44 (14.73)	
Stage IV	47	39.22 (17.36)	
BMD, mean (S.D.)			
Normal	22	45.68 (19.78)	0.020
Osteopenia	42	42.45 (13.18)	
Osteoporosis	42	35.55 (14.38)	

[a]*P*-values were from ordinal logistic regressions after adjustment for age, sex, BMI and disease duration. 25(OH)D: 25-hydroxyvitamin D.

The IL-23/IL-17 axis drives immune activation and chronic inflammation through the differentiation and activation of Th17 cells and has been proposed to play an important role in RA [28]. Indeed, we confirmed that levels of both IL-17 and IL-23 were evaluated in RA patients in our study. Several *in vitro* studies revealed that vitamin D could regulate this axis. van Hamburg *et al.* [29] reported that $1,25(OH)_2D_3$ significantly suppressed autocrine IL-17A production in Th17–RA synovial fibroblast co-cultures and synovial biopsy cultures. Collin *et al.* [30] reported that $1,25(OH)_2D_3$ reduced IL-17A levels in stimulated peripheral blood mononuclear cells from treatment-naive patients with early RA. Pedersen *et al.* [31] reported that $1,25(OH)_2D_3$ inhibited the secretion of IL-23 in dendritic cells. In our *in vivo* study we found that serum concentrations of 25(OH)D were significantly and negatively associated with IL-17 and IL-23, suggesting that vitamin D may have anti-inflammatory and immunoregulatory effects through inhibition of the Th17 response in RA.

It is well known that vitamin D is good for bone health and is effective for the prevention and treatment of OP. We found that in patients with RA, OP was highly prevalent and was associated with reduced 25(OH)D levels. This is consistent with the findings from a previous study [32]. We failed to find significant associations between 25(OH)D level and bone erosion in RA patients.

This study has several potential limitations. First, this study utilized case–control and cross-sectional designs, so the causal relationship is unknown. Future cohort studies will be required to determine this. Second, we only recruited 130 RA patients. This sample size may not have enough power to determine a significant association between 25(OH)D and radiographic progression. Third, we did not record other factors, such as smoking and medications, so we cannot exclude potential confounding effects from these factors. We did not measure the free (bioavailable) vitamin D and vitamin D–binding protein [4], which may be more important than serum 25(OH)D in the pathogenesis of RA.

In conclusion, we report that 25(OH)D levels were reduced in patients with RA and were negatively associated with disease activity, IL-17/IL-23 and bone loss in RA, suggesting that vitamin D deficiency may play a role in the aetiology of RA.

Rheumatology key messages

- Serum levels of 25(OH)D were lower in the RA group than in the control group.
- In RA patients, serum 25(OH)D levels were negatively associated with disease activity and serum levels of IL-17 and IL-23.
- In RA patients, serum 25(OH)D levels were lower in those with osteopenia and osteoporosis than in those with normal BMD.

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Clinical vignette

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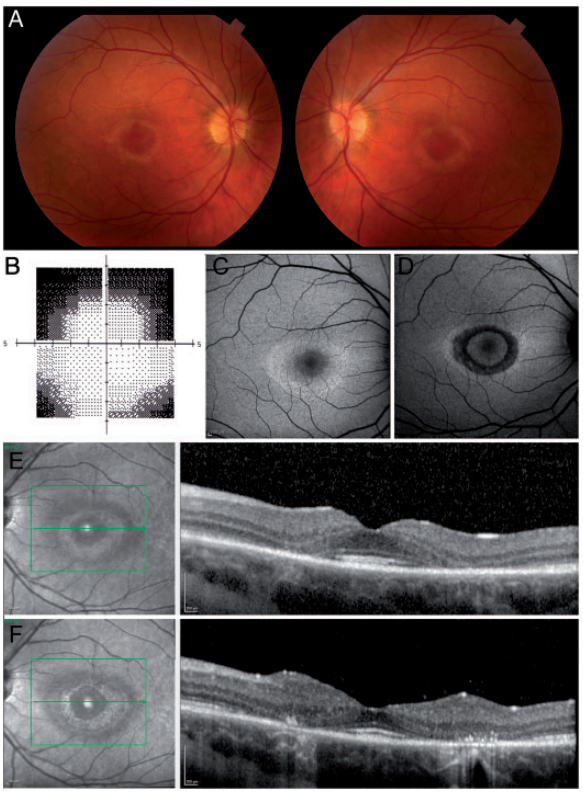
Retinal toxicity found in a patient with systemic lupus erythematosus prior to 5 years of treatment with hydroxychloroquine

A 19-year-old Caucasian male diagnosed with SLE with renal failure was started on HCQ 200 mg p.o. twice a day. His weight was 62.3 kg and he took 6.4 mg/kg. The patient had retinal examinations twice a year elsewhere. Four years and 4 months after starting HCQ, the patient had a bull's eye maculopathy (Fig. 1A) and abnormal visual fields (Fig. 1B). Damage was seen on autofluorescence (Fig. 1C) and optical coherence tomography (OCT; Fig. 1E). Although he had objective retinal damage, he had no visual complaints and his uncorrected visual acuity was 20/20 in each eye. Despite discontinuation of HCQ, he continued to show progression of retinal damage 3 years later (Fig. 1D and F).

The American Academy of Ophthalmology released revised recommendations on screening for chloroquine and HCQ retinopathy in 2011, which include screening with objective tests such as spectral domain OCT, multifocal electroretinogram and fundus autofluorescence [1]. They recommend dosing by ideal body weight and not actual weight. Usually damage is seen with long-term therapy and doses >6.5 mg/kg. This patient demonstrates that with renal failure, retinal toxicity can be seen in <5 years on doses <6.5 mg/kg [2].

Fig. 1 Retinal imaging



(**A**) Fundus photographs at diagnosis of retinal toxicity. (**B**) Visual field macular study at diagnosis of retinal toxicity. (**C**) Autofluorescence at diagnosis of retinal toxicity. (**D**) Autofluorescence 3 years after diagnosis of retinal toxicity. (**E**) OCT at diagnosis of retinal toxicity. (**F**) OCT 3 years after diagnosis of retinal toxicity. OCT: optical coherence tomography.

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