


BMJ Open Association between vitamin D and fatigue in patients with rheumatoid arthritis: a cross-sectional study

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ABSTRACT

Objectives In rheumatoid arthritis (RA), fatigue is an important complaint with a significant impact on quality of life. Vitamin D has modulatory effects on cells of the immune system and may potentially affect RA disease activity and thereby RA-related fatigue. The purpose of this study was to explore associations between fatigue and vitamin D status in patients with RA.

Design Hypothesis-generating cross-sectional study.

Setting Scheduled follow-up visits at a hospital-based general rheumatology clinic.

Participants Patients (n=169) with established RA.

Primary outcome measures and analyses Fatigue, assessed by the Chalder fatigue questionnaire, and serum concentrations of 25-hydroxyvitamin D (25(OH)D), assessed by liquid chromatography–tandem mass spectrometry. Associations were analysed by correlation, and multivariate linear regression with adjustments for age, sex, body mass index, RA disease activity as measured by the Disease Activity Score 28-joint count C reactive protein (DAS28-CRP), psychological distress, pain and sleep. Fatigue was also compared across four groups based on the levels of serum 25(OH)D with cut points at 30, 50 and 75 nmol/L using one-way analysis of variance.

Results Two-thirds of the patients (116/169, 69%) were classified with low RA disease activity, that is, a DAS28-CRP score below 3.2. Their mean (SD) serum 25(OH)D concentration was 56.3 (21.2) nmol/L, with 77 (45.6%) having values below 50 nmol/L and 12 patients (7.1%) below 30 nmol/L. The correlation between fatigue and serum concentrations of 25(OH)D was weak and not statistically significant, $r = -0.14$ (95% CI: -0.29 to 0.03 , $p=0.08$). In the multivariate model, fatigue was significantly associated with RA disease activity, psychological distress and pain, but not with serum 25(OH)D. Fatigue did not differ across groups with varying levels of serum 25(OH)D.

Conclusion This cross-sectional study found no evidence of association between vitamin D and fatigue in patients with RA.

BACKGROUND

In rheumatoid arthritis (RA), fatigue is an important complaint with a significant impact on quality of life.¹ RA patients rank fatigue as one of their most disabling symptoms, and measures of fatigue provides information central to the understanding of the outcome

Strengths and limitations of this study

- This study used validated measures of fatigue, rheumatoid arthritis (RA) disease activity, pain, sleep and psychological distress, and vitamin D status was analysed by liquid chromatography–tandem mass spectrometry.
- The variability in fatigue scores and serum 25-hydroxyvitamin D was substantial, ensuring robust correlation and regression analyses.
- The sample (n=169) was representative for patients with established RA; nearly all patients received disease-modifying antirheumatic drug treatment, and 89% met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA when applied retrospectively.
- The study was performed at a single centre using a sample of convenience.

of this disease.^{2,3} The cause of fatigue in RA is not well known; studies on the relationship with inflammation have yielded inconsistent results and many patients continue to experience fatigue even after achieving remission or low disease activity.^{4,5} In patients with RA, as well as in other clinical conditions and in the general population, fatigue correlates with pain, anxiety, depression, sleep disturbance and obesity.^{6–10}

Vitamin D has both direct and indirect modulatory effects on cells of the immune system.¹¹ It has been hypothesised that vitamin D deficiency could contribute to increased immune activation, thus playing a role in RA pathogenesis.¹² Systematic reviews have found evidence for a negative association between serum vitamin D and RA disease activity.^{13,14} Whether vitamin D status is linked to fatigue in RA is unknown.

An established marker for vitamin D status is the serum concentration of 25-hydroxyvitamin D (25(OH)D), representing both dietary and skin-synthesised vitamin D. Currently no consensus exists on the optimal level of serum of 25(OH)D. Suggested thresholds for

vitamin D deficiency vary from 30 to 50 nmol/L, whereas serum concentrations between 50 and 75 nmol/L have been suggested to represent vitamin D insufficiency.^{15–18} Of note, 1 nmol/L 25(OH)D corresponds to 0.4 ng/mL.

While vitamin D status in RA patients has been investigated with regard to depression and anxiety,¹⁹ studies into the potential association with fatigue remain scarce. Since effective interventions against fatigue remain elusive, there is a need for hypothesis-generating research into potential modifiable sources of fatigue in RA. The aim of the current study was to explore cross-sectional associations between fatigue and vitamin D status in patients with RA.

METHODS

Patient and public involvement

Patients or the public were not involved in the design of the study.

Patients, setting and procedures

This cross-sectional study took place at the Department of Rheumatology, Østfold Hospital Trust, a general rheumatology clinic in south-east Norway responsible for services for approximately 300 000 people. Patients were consecutively recruited by the hospital staff during scheduled follow-up visits to the clinic. Written informed consent was obtained from all participants. Inclusion criteria were age ≥ 18 years, a clinical diagnosis of RA and ability to read and understand Norwegian. Clinical information from history and examination was collected and reported by trial care givers (physicians or nurses) at the inclusion in the study. The recruitment started in September 2013 and was completed in June 2015. All data were collected at the date of inclusion in the study.

Instruments and assessments

Background and clinical characteristics

Patients provided information on their educational, work and smoking status. Years since the diagnosis of RA and current disease-modifying antirheumatic drug (DMARD) treatment, including oral glucocorticoids, were obtained from patients' medical records.

The 2010 ACR/EULAR classification criteria for RA²⁰ were retrospectively applied by chart review by an experienced rheumatologist (AJH), using a score of ≥ 6 to classify definite RA. RA disease activity was assessed by the Disease Activity Score 28-joint count C reactive protein (DAS28-CRP) based on the number of swollen and tender joints, a visual analogue scale of general health and C reactive protein (CRP; mg/L).^{21 22} The DAS28-CRP ranges from 0 to 9.4, scores below 3.2 are considered representing low disease activity.²³

Body mass index (BMI) was calculated as weight in kilograms divided by height in square metres.

Psychological distress was assessed by the Hospital Anxiety and Depression Scale (HADS).^{24 25} The HADS consists of one scale for depression and one for anxiety,

each comprising seven items which are scored from 0 to 3. The total score ranges from 0 to 42, higher scores indicate an increased level of symptoms.

Sleep disturbance was assessed by the first dimension of the Basic Nordic Sleep Questionnaire²⁶ ('Have you had difficulties falling asleep during the last 3 months') on a five-point Likert scale ranging from 1 (never or less than once per month) to 5 (every night or almost daily).

Pain severity was assessed by the average pain last 24 hours item of the Brief Pain Inventory²⁷ on a numerical rating scale from 0 (no pain) to 10 (pain as bad as you can imagine).

Fatigue

Fatigue was assessed by the Chalder fatigue questionnaire (CFQ)^{28 29} The CFQ asks about fatigue symptoms experienced during the last 4 weeks including two scales, physical fatigue (seven items) and mental fatigue (four items). All items are scored on a four-point Likert scale, and the sum score produces the total fatigue score ranging from 0 to 33. Higher scores indicate more fatigue. The CFQ has been used to assess fatigue in the Norwegian general population and in a variety of clinical settings.^{30 31}

Vitamin D measurement

Serum 25(OH)D refers to the sum of the concentrations of the metabolites 25(OH)D₂ and 25(OH)D₃. Analysis with determination of 25(OH)D₂/D₃ was performed consecutively at the Hormone laboratory at the Department of Medical Biochemistry, Oslo University Hospital, using an in-house liquid chromatography–tandem mass spectrometry method. In brief, after protein precipitation, 25(OH)D was extracted from samples using phospholipid depletion plates. Separation was achieved by reversed-phase chromatography and the isobaric C3 epimer 3-epi-25(OH)D₃ was separated from 25(OH)D₃. Mass spectrometric detection was performed by electrospray ionisation and triple quadrupole ion separation (multiple reaction monitoring). The laboratory participated in the Vitamin D External Quality Assessment Scheme³² for total 25(OH)D is accredited by the Norwegian Accreditation as a testing laboratory, and it complies with the general requirements for the competence of testing and calibration laboratories (ISO/IEC 17025:2017). The total analytical variation, expressed as relative SD, was below 13%.

Analysis

Associations between fatigue and vitamin D were analysed by correlation (Pearson *r* with bootstrap 95% CI) and multivariate linear regression. The multivariate analysis was performed using total fatigue score as dependent variable, and serum 25(OH)D, age, sex, BMI, RA disease activity, psychological distress, pain and sleep disturbance as independent variables. Assumptions underlying linear regression analysis regarding normality and linearity were adequately met, and all variance inflation factors were below 2.

In order to investigate potential threshold effects of serum 25(OH)D on fatigue, patients were categorised into four groups: (1) <30 nmol/L, (2) 30–49 nmol/L, (3) 50–74 nmol/L and (4) ≥75 nmol/L. The cut points were based on the increased risk of rickets/osteomalacia at serum levels below 30 nmol/L, and the uncertainty in the literature as to whether 50 nmol/L or 75 nmol/L represents safe and sufficient 25(OH)D levels. A one-way analysis of variance (ANOVA) was conducted to compare fatigue across these groups.

P values <0.05 were considered statistically significant; all tests were two-sided. Analyses were performed by IBM SPSS Statistics for windows V25.0 (IBM Corp.).

RESULTS

In total 208 patients were consecutively invited to participate in the study, of whom 178 (86 %) gave written informed consent. Six patients were excluded due to missing data, and three were excluded due to an incorrect RA diagnosis, leaving 169 patients available for analyses.

Clinical and socio-demographic characteristics are presented in [table 1](#).

The sample included patients with established disease with a median (IQR) disease duration of 9 (4–17.5) years. Nearly all patients (155/169, 92%) received synthetic and/or a biologic DMARD treatment, and/or oral glucocorticoids. Of 22 patients taking oral glucocorticoids, 5 patients did not receive a DMARD. Two-thirds (116/169, 69%) were classified with low RA disease activity, that is, a DAS28-CRP score below 3.2. In total 89% (149/167) met the retrospectively applied 2010 ACR/EULAR classification criteria for RA.

Patients' mean (SD) serum 25(OH)D was 56.3 (21.2) nmol/L, with 77 (46%) having a serum 25(OH)D concentration below 50 nmol/L and 12 patients (7%) having a serum 25(OH)D below 30 nmol/L. The mean (SD) fatigue score was 15.2 (4.8).

The correlation between fatigue and serum concentrations of 25(OH)D was weak and not statistically significant, $r = -0.14$ (95% CI: -0.29 to 0.03 , $p = 0.08$) ([figure 1](#)). In the multivariate analysis, fatigue was significantly associated with RA disease activity, psychological distress and pain, but not with serum 25(OH)D ([table 2](#)). Fatigue scores did not differ across varying levels of serum 25(OH)D (ANOVA; $F(3.165) = 1.05$, $p = 0.37$) ([figure 2](#)).

DISCUSSION

In this cross-sectional study of patients with established RA, fatigue was not associated with vitamin D status. We are not aware of other studies of vitamin D and fatigue in RA, but the lack of association is consistent with previous studies in systemic lupus erythematosus,^{33 34} inflammatory bowel disease³⁵ and multiple sclerosis.³⁶ A Mendelian randomisation study did not find genetic evidence for a causal effect of 25(OH)D on fatigue.³⁷ Vitamin D supplementation did not improve fatigue in patients with breast

Table 1 Patient characteristics (n=169)

Females, n (%)	123 (72.8)
Age, years, mean (SD)	58.4 (11.2)
College or university education (≥4 years), n (%)	48 (28.4)
Full-time or part-time work, n (%)	51 (30.2)
Current smoker, n (%)	23 (13.6)
Body mass index, mean (SD)	26.4 (4.1)
Years since RA diagnosis, median (IQR)	9 (4.0–17.5)
DAS28-CRP, mean (SD)	2.9 (1.3)
Low RA disease activity (DAS28-CRP<3.2), n (%)	116 (68.6)
Concomitant DMARDs	
Synthetic DMARDs only, n (%)	69 (40.8)
Synthetic and biologic DMARDs, n (%)	60 (35.5)
Biologic DMARDs only, n (%)	21 (12.4)
Oral glucocorticoids only, n (%)	5 (3.0)
None, n (%)	14 (8.3)
Fatigue* (0–33), mean (SD)	15.2 (4.8)
Pain† (0–10), median (IQR)	4 (2–5)
Sleep disturbance‡ (0–5), median (IQR)	2 (2–3)
Psychological distress§ (0–42), median (IQR)	7 (3.75–11.0)
Serum 25(OH)D, nmol/L, mean (SD)	56.3 (21.2)
Serum 25(OH)D	
<30 nmol/L, n (%)	12 (7.1)
30–49 nmol/L, n (%)	65 (38.5)
50–74 nmol/L, n (%)	67 (39.6)
≥75 nmol/L, n (%)	25 (14.8)

*Chalder fatigue questionnaire.

†Brief Pain Inventory average pain (last 24 hours).

‡Basic Nordic Sleep Questionnaire.

§Hospital Anxiety and Depression Scale.

CRP, C reactive protein; DAS28-CRP, Disease Activity Score 28-joint count CRP; DMARDs, disease-modifying antirheumatic drugs; 25(OH)D, 25-hydroxyvitamin D; RA, rheumatoid arthritis.

cancer³⁸ or chronic fatigue syndrome,³⁹ nor in primary care patients with mild to moderate vitamin D deficiency.⁴⁰ A small effect of supplementation was reported in otherwise healthy individuals.⁴¹

Our results are in line with a well-established association between fatigue and psychological distress.⁴ They also support previous findings of correlation with RA disease activity and pain.⁶ As expected, the mean level of fatigue in this cohort was higher than what has been reported from general population samples.^{30 42 43}

In this cohort, nearly half of the subjects had serum 25(OH)D concentrations below 50 nmol/L. Comparing our results with other populations or samples is complicated due to varying sun exposure, skin pigmentation, ethnicity, vitamin D intake/supplementation and analytical methodology.^{44 45} In two samples from the general Norwegian population, 28% and 70% had serum 25(OH)

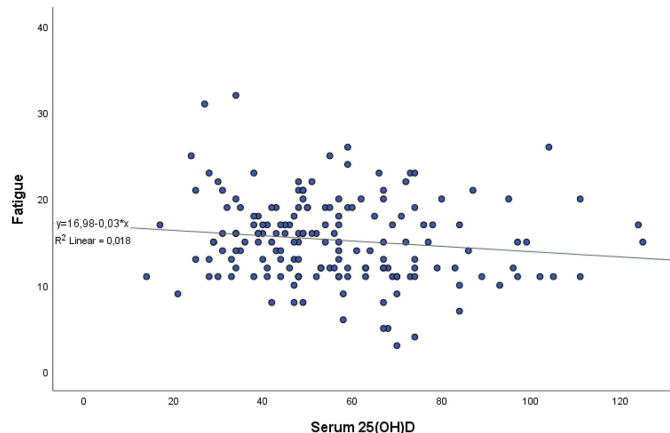


Figure 1 Relationship between fatigue and serum 25(OH)D. 25(OH)D, 25-hydroxyvitamin D.

D below 50 nmol/L.^{44 46} Whether RA patients in general have lower levels of 25(OH)D than healthy controls is unsettled.^{13 47}

The strengths of this study are the use of validated measures of fatigue as well as RA disease activity, pain, sleep and psychological distress. Vitamin D status was analysed by liquid chromatography–tandem mass spectrometry, a method considered reference standard in the measurement of serum 25(OH)D.⁴⁸ It was performed at a single centre using a sample of convenience but we believe that the setting was appropriate for the purpose, namely to generate hypotheses on the association between vitamin D and fatigue in RA. The proportion of patients who met the 2010 ACR/EULAR classification criteria for RA (89%) was similar to validation studies using diagnosis by a rheumatologist as reference standard.⁴⁹ Socio-demographic characteristics, disease activity and drug therapy were also very similar to RA patients treated in Norwegian rheumatology clinics at that period.^{50 51} Furthermore, the variability in fatigue scores and serum 25(OH)D was substantial, ensuring robust correlation analyses. Among

Table 2 Multiple linear regression model for fatigue

	β	95% CI	P value
Serum 25(OH)D	-0.01	-0.04 to 0.02	0.66
Age	-0.03	-0.08 to 0.03	0.31
Sex	-0.26	-1.59 to 1.06	0.70
Body mass index	0.03	-0.13 to 0.18	0.74
DAS28-CRP	0.66	0.14 to 1.18	0.01
Psychological distress*	0.32	0.21 to 0.44	<0.001
Pain†	0.47	0.14 to 0.79	0.01
Sleep disturbance‡	0.11	-0.47 to 0.69	0.71

*Hospital Anxiety and Depression Scale.

†Brief Pain Inventory average pain (last 24 hours).

‡Basic Nordic Sleep Questionnaire.

DAS28-CRP, Disease Activity Score 28-joint count C reactive protein; 25(OH)D, 25-hydroxyvitamin D.

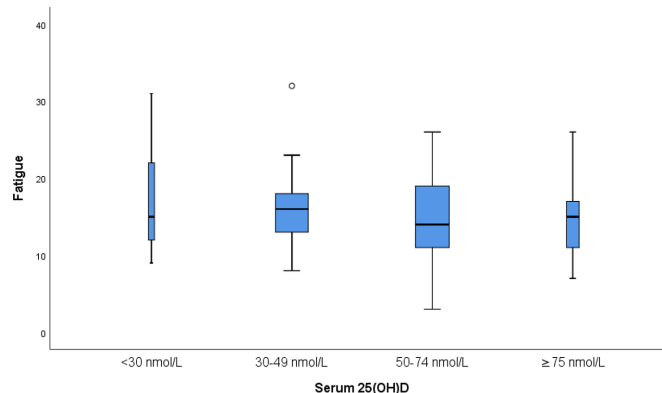


Figure 2 Fatigue according to vitamin D levels. Total range (whiskers), medians (horizontal lines) and 25%–75% IQRs (boxes) of fatigue. Box widths are scaled according to counts.

the limitations of this study are those inherent to cross-sectional studies such as unknown temporal sequence of associated factors. Our sample included patients with established RA and the results do not apply to those with very early disease.

In conclusion, this hypothesis-generating cross-sectional study found no basis for vitamin D to be associated with fatigue in patients with established RA.

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Contributors LPJ-J conceived, designed and led the study. AJH acquired the data. LG performed the analyses and wrote the manuscript. All authors participated in the interpretation of the results and critical revision of the manuscript and they gave final approval of the version to be published. LPJ-J is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the Norwegian Regional Ethics Committee South East (2012/845/REK).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon request.

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