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Association Between Vitamin D Deficiency and Disease Activity, Disability, and Radiographic Progression in Early Rheumatoid Arthritis: The ESPOIR Cohort

Gaël Mouterde[1], Etienne Gamon[1], Nathalie Rincheval[2], Cédric Lukas[1], Raphaele Seror[3], Francis Berenbaum[4], Anne-Marie Dupuy[5], Claire Daien[1], Jean-Pierre Daurès[2], and Bernard Combe[1]

ABSTRACT. ***Objective.*** To evaluate the association of baseline serum level of vitamin D with disease activity, disability, and radiographic damage over the first year in early rheumatoid arthritis (RA).

Methods. Among early arthritis patients included in the ESPOIR cohort, patients with early RA were evaluated. Levels of 25-hydroxy vitamin D2 and D3 were measured at baseline. Baseline associations between vitamin D level and 28-joint count Disease Activity Score based on erythrocyte sedimentation rate (DAS28-ESR), Health Assessment Questionnaire–Disability Index (HAQ-DI), and van der Heijde modified total Sharp score (mTSS) were assessed. Bivariate analysis was used to assess the association between vitamin D level and radiographic progression (mTSS increased by ≥ 1 point) or disability (HAQ-DI ≥ 0.5) over 12 months. Forward stepwise multiple logistic regression was used to evaluate the independent association of baseline variables and outcomes.

Results. Among 813 patients with early arthritis, data for 645 patients with RA were analyzed. Vitamin D level was < 10 ng/mL (deficiency, group 1), 10–29.9 ng/mL (low level, group 2), and ≥ 30 ng/mL (normal, group 3) for 114 (17.7%), 415 (64.54%), and 114 (17.7%) patients, respectively. At baseline, DAS28-ESR and HAQ-DI were higher with vitamin D deficiency compared with groups 2 and 3 combined (P = 0.007 and P = 0.001, respectively), as was mean mTSS, but not significantly (p = 0.076). On multivariate analysis, baseline vitamin D deficiency was associated with HAQ-DI at 6 months (OR 1.70) and mTSS at 12 months (OR 1.76).

Conclusion. Vitamin D deficiency was associated with more active and severe disease at baseline and may predict disability and radiographic progression over 1 year in early RA patients. [ClinicalTrials.gov: NCT03666091]

Key Indexing Terms: disease activity, disability, early arthritis, rheumatoid arthritis, severity, vitamin D

The management of early arthritis is crucial for rheumatologists and is codified by international recommendations[1]. Nevertheless, we still need to better identify patients at risk of early radiographic damage, to closely adapt treatment or propose early intensive therapy to prevent disease progression. Numerous studies have identified prognostic factors associated with worse radiographic outcome[2,3], such as early erosion, high acute-phase reactants, or rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA).

Environmental factors such as tobacco use play an essential role in the pathogenesis of rheumatoid arthritis (RA)[4]. Serum level of vitamin D may also have a role, as suggested by a north/south prevalence gradient of RA[5]. A study showed that patients with low vitamin dietary daily intake were at risk of RA[6] and some more recent studies underlined the possible link between low serum vitamin D level and high disease activity[7,8,9] or disability[10] in patients with RA. We previously found radiographic damage in the short term in early arthritis patients with seasonal symptom onset during winter or spring[3].

These data led us to study the effect of vitamin D serum level on disease activity and severity in a large inception cohort of patients with early RA. The main objective was to assess the association of baseline serum 25-hydroxy vitamin D2 and D3 [25(OH)D] level with disease activity measured by the 28-joint

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[1]G. Mouterde, MD, E. Gamon, MD, Cedric Lukas, MD, PhD, C. Daien, MD, Bernard Combe, MD, PhD, Rheumatology Department, CHU Montpellier, University of Montpellier, Montpellier; [2]N. Rincheval, J.P. Daurès, MD, PhD, Biostatistics, University Institute of Clinical Research, EA 2415, Montpellier; [3]R. Seror, MD, PhD, Rheumatology, Hôpital Kremlin Bicêtre, Paris; [4]F. Berenbaum, MD, PhD, Sorbonne Université, INSERM, DHU i2B, AP-HP, Hôpital Saint-Antoine, F-75012, Paris; A.M. Dupuy, MD, Department of Biochemistry, CHU Montpellier, Montpellier, France.

Address correspondence to Dr. G. Mouterde, Rheumatology Department, Lapeyronie Hospital, 371 avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, France. Email: g-mouterde@chu-montpellier.fr.

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count Disease Activity Score based on erythrocyte sedimentation rate (DAS28-ESR), disability by the Health Assessment Questionnaire–Disability Index (HAQ-DI), and radiographic damage by the van der Heijde modified total Sharp score (mTSS) at baseline in early RA patients in the ESPOIR cohort. The secondary objective was to assess the link between baseline 25(OH)D level and functional disability or radiographic progression during the first year.

MATERIALS AND METHODS

Study population. The ESPOIR cohort included 813 patients with early arthritis from 14 French rheumatology centers between 2002 and 2005[11] (ClinicalTrials.gov: NCT03666091). Patients had 2 or more swollen joints for more than 6 weeks and less than 6 months. They should not have received disease-modifying antirheumatic drugs (DMARD) or steroids for more than 2 weeks, and these drugs should have been stopped at least 2 weeks before inclusion. Patients with a definite diagnosis different from RA were excluded. Patients were evaluated every 6 months for 2 years and then once a year, and received routine treatment from their rheumatologist. Only patients who met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA at baseline were selected for our current study. The protocol of the ESPOIR cohort was approved by the ethics committee of Montpellier, France (no. 020307), and all patients gave their signed informed consent before inclusion.

Vitamin D assessment. Serum 25(OH)D level was measured in the baseline blood sample from patients. Measurement involved an immunochemiluminescence assay (ng/mL; Roche-Cobas 8000, Roche) performed in a central laboratory (Biochemical Department, Lapeyronie Hospital). Vitamin D level was considered normal at ≥ 30 ng/mL, insufficient at 10–29.9 ng/mL, and deficient at < 10 ng/mL.

Clinical and biological assessment. The following information was collected at baseline and at each visit: demographic data, socioeconomic data, comorbidities, tobacco use, alcohol consumption, duration of symptoms at first visit, and season of first symptoms (defined by the date of the first fixed swollen joint), number of tender and swollen joints, patient's global assessment (PtGA) on a 0–100 visual analog scale (VAS), ESR, C-reactive protein (CRP) level, DAS28-ESR, functional disability evaluated by the HAQ-DI (a score ≥ 0.5 considered relevant disability), quality of life evaluated by the Medical Outcomes Study Short Form-36 (SF-36), and socioeconomic status evaluated by familial income. RF and ACPA (anticyclic citrullinated peptide 2)[11] were tested at baseline.

Radiographic evaluation. Radiographs of hands, wrists, and forefeet were taken at baseline and 6 and 12 months. They were centralized and scored according to the van der Heijde mTSS[12] by an experienced imaging reader (CL) who was blinded to the patient's other data, in known chronological order. Radiographic progression was defined by an increase of at least 1 unit in the mTSS.

Statistical analysis. Univariate analysis of the association between vitamin D level and outcome measures (DAS28, HAQ-DI, mTSS) involved Pearson chi-square test or Fisher's exact test. Continuous variables were selected by Mann-Whitney test or transformed to categorical variables in case of cutoff provided by the manufacturer for biological data. Logistic regression analysis was used to determine independent baseline variables predicting 6- and 12-month outcomes. The explanatory variables included in the model were significant on univariate analysis. A forward stepwise procedure was used to select variables included in the model, with $P = 0.2$ for inclusion and 0.05 for exclusion. OR and 95% CI were estimated. $P < 0.05$ was considered statistically significant for variables in the multivariate model. SAS v9.4 (SAS Institute Inc.) was used for analysis.

RESULTS

Patient characteristics. In total, 645 patients (79.34%) fulfilled the 2010 ACR/EULAR criteria for RA at baseline, and vitamin D data were available for 643 (2 missing data). Baseline characteristics of patients are shown in Table 1. Overall, 7 (1.09%), 43 (7.17%), and 37 patients (6.30%) had vitamin D supplementation at baseline, 6 months, and 12 months, respectively. HAQ-DI ≥ 0.5 at baseline, 6 months, and 12 months, and radiographic progression at 12 months were similar for supplemented patients and the whole population (data not shown).

Analysis of 25(OH)D. Baseline mean (SD) serum vitamin D level was 20.55 (11.10) ng/mL. In total, 114 (17.73%), 415 (64.54%), and 114 (17.73%) patients had baseline serum vitamin D level < 10 ng/mL (deficiency, group 1), 10–29.9 ng/mL (low level, group 2), and ≥ 30 ng/mL (normal, group 3), respectively. For most of the outcome measures, the normal group did not differ from the low-level group. Therefore, we combined those 2 groups for analysis. Baseline vitamin D distribution was bimodal and not Gaussian (Supplementary Figure 1, available with the online version of this article). As expected, vitamin D supplementation was less frequent in group 1 than groups 2 and 3 at baseline ($P = 0.019$). Proportion of patients with vitamin D deficiency was more important in winter and spring as compared to summer and fall [44/170 (25.88%), 14/152 (9.21%), 21/144 (14.58%), and 35/177 (19.77%) respectively; $P < 0.001$]. Baseline

Table 1. Baseline characteristics of the study population with early RA (2010 ACR/EULAR criteria; n = 645).

Characteristics	Values
Female, n (%)	497 (77.05)
Age, yrs, mean (SD)	48.80 (12.22)
White, n (%)	592 (91.78)
Symptom duration at first visit, days, mean (SD)	102 (52)
25(OH)D level, ng/mL, mean (SD), n = 643	20.55 (11.10)
25(OH)D categories, ng/mL, n (%), n = 643	
< 10 (group 1)	114 (17.73)
10–29.9 (group 2)	415 (64.54)
≥ 30 (group 3)	114 (17.73)
DAS28, mean (SD)	5.38 (1.23)
HAQ-DI, mean (SD)	1.05 (0.69)
mTSS, mean (SD)	6.46 (8.17)
Current smoker, n (%)	136 (21.09)
Alcohol consumption, n (%)	117 (18.14)
*HLA-DRB1*01* or *04* gene, n (%)	353 (57.40)
CRP, mg/L, mean (SD), n < 10 mg/L	21.29 (33.42)
ESR, mm/h, mean (SD), n < 10 mm/h	30.56 (24.91)
ACPA positivity (anti-CCP antibody), n (%)*	314 (48.68)
IgM-RF positivity, n (%)§	365 (56.59)
25(OH)D supplementation, n (%)	7 (1.09)

* Positive if > 50 IU/mL. § Positive if > 9 IU/mL. RA: rheumatoid arthritis; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; 25(OH)D: 25-hydroxy vitamin D2 and D3; DAS28: 28-joint count Disease Activity Score; HAQ-DI: Health Assessment Questionnaire–Disability Index; mTSS: van der Heijde modified total Sharp score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ACPA: anticitrullinated protein antibodies; CCP: cyclic citrullinated peptide; RF: rheumatoid factor.

variables associated with vitamin D deficiency are presented in Supplementary Table 1 and Supplementary Table 2.

Disease activity. At baseline, mean (SD) DAS28 was higher with vitamin D deficiency than groups 2 and 3 combined [5.65 (1.39) vs 5.33 (1.19), $P = 0.007$]. As compared with groups 2 and 3, vitamin D deficiency was associated but not significantly with DAS28 > 5.1 (66% vs 56%; OR 1.52, 95% CI 0.99–2.33; $P = 0.055$) and was significantly associated with increased baseline ESR (OR 2.67, 95% CI 1.76–4.05; $P < 0.0001$) and CRP level (OR 1.64, 95% CI 1.09–2.47; $P = 0.018$) but was not among the baseline predictors of disease activity on multivariate analysis of predictors of disease activity at baseline.

Functional outcome. Mean (SD) HAQ-DI was higher with vitamin D deficiency than groups 2 and 3 combined at baseline [1.24 (0.73) vs 1.01 (0.67), $P = 0.001$], 6 months [0.75 (0.65) vs 0.53 (0.56), $P = 0.002$] and 1 year [0.68 (0.67) vs 0.51 (0.57), $P = 0.027$]. At Month 6, as compared with groups 2 and 3, vitamin D deficiency was associated with HAQ-DI ≥ 0.5 (61.2% vs 45.8%; OR 1.87, 95% CI 1.20–2.91; $P = 0.006$), but the same observation at Month 12 was not significant (55% vs 44.6%; OR 1.52, 95% CI 0.98–2.34; $P = 0.062$).

At Month 6, stepwise logistic regression analysis revealed vitamin D deficiency as the strongest predictor of HAQ-DI ≥ 0.5 (OR 1.70, 95% CI 1.05–2.76, $P = 0.031$). Other independent predictors of poor functional outcome were female sex, PtGA, physical component of SF-36, and IgM-RF positivity (Table 2). Socioeconomic status, assessed by familial income, was not selected as an independent variable in this model. Vitamin D level was not an independent predictor of functional outcome at 12 months.

Radiographic outcome. At baseline, mean (SD) mTSS was higher but not significantly with vitamin D deficiency than the 2 other groups [8.16 (10.09) vs 6.14 (7.73), $P = 0.076$]. At 6 months and 1 year, mean (SD) mTSS was significantly higher with vitamin D deficiency than groups 2 and 3 [9.80 (11.66) vs 6.99 (8.96) and 10.38 (13.37) vs 7.73 (10.57), $P = 0.014$ and $P = 0.033$, respectively]. At 12 months, as compared with groups 2 and 3, vitamin D deficiency was associated with radiographic progression [mean (SD) radiographic progression 1.99 (4.54) vs 1.66 (4.67), $P = 0.015$; OR 1.90, 95% CI 1.19–3.03, $P = 0.007$] and erosion score progression (OR 1.89, 95% CI 1.18–3.03; $P = 0.007$) but not joint space narrowing progression (OR 1.87, 95% CI 0.93–3.75; $P = 0.067$).

Stepwise logistic regression analysis of predictive factors of the progression of mTSS at 12 months showed that ACPA, IgA-RF positivity, baseline mTSS, PtGA, and 25(OH)D deficiency were associated with radiographic outcome at 12 months (Table 3).

Table 2. Logistic regression analysis of independent baseline variables associated with disability (HAQ-DI score ≥ 0.5) at Month 6.

AUC = 0.728	OR (95% CI)	$P^{\S}$
25(OH)D level, ng/mL, < 10 vs ≥ 10	1.70 (1.05–2.76)	0.031
Sex, female vs male	1.74 (1.15–2.63)	0.008
PtGA (VAS)	1.01 (1.00–1.02)	0.003
IgM-RF positivity, IU/mL*	0.63 (0.44–0.89)	0.009
SF-36 physical component	0.94 (0.92–0.96)	< 0.001

Baseline variables included in the model: 25(OH)D level, sex, PtGA, VAS, TJC, SJC, IgA-RF, IgM-RF, physical component of SF-36. § Chi-square test. * Positive if > 9 IU/mL. HAQ-DI: Health Assessment Questionnaire–Disability Index; AUC: area under the curve; 25(OH)D: 25-hydroxy vitamin D2 and D3; PtGA: patient's global assessment; VAS: visual analog scale; RF: rheumatoid factor; TJC: tender joint count; SJC: swollen joint count; SF-36: Medical Outcomes Study Short Form-36.

DISCUSSION

Vitamin D has always been of great interest for rheumatologists. Its implication in phosphocalcic metabolism has led to its routine testing. More recently, studies have shown its immunologic properties, particularly in rheumatic conditions such as RA. The primary objective of the current study was to assess the association of baseline vitamin D with disease activity and severity during the first year in a large cohort of early RA patients. In our cohort, the mean baseline serum level of vitamin D was low, and most patients showed at least vitamin D insufficiency. At baseline, disease activity and functional and radiographic outcome were worsened with vitamin D deficiency. The secondary objective was to assess the link between vitamin D level and functional disability or radiographic progression during the first year. In addition to other known factors such as RF or ACPA, baseline vitamin D deficiency was an independent predictor of worse radiographic outcome at 12 months. Vitamin D deficiency associated with more active and severe disease at baseline may predict disability and radiographic progression over 1 year in early RA patients.

The finding of low baseline serum vitamin D level and at least vitamin D insufficiency in most patients is globally consistent with findings in other RA cohorts[13] and in studies evaluating

Table 3. Logistic regression analysis of independent baseline variables associated with van der Heijde modified total Sharp score (mTSS) progression at Month 12 (including baseline mTSS).

AUC = 0.799	OR (95% CI)	$P^{\S}$
25(OH)D level, ng/mL, < 10 vs ≥ 10	1.76 (1.01–3.06)	0.045
ACPA positivity, IU/mL*	2.31 (1.32–4.03)	0.0032
IgA-RF positivity, IU/mL†	2.79 (1.56–4.98)	< 0.001
Baseline mTSS	1.11 (1.07–1.14)	< 0.001
PtGA on a VAS	0.99 (0.98–0.998)	0.012

Baseline variables included in the model: ACPA, IgM-RF, IgA-RF, ESR, CRP level, 25(OH)D level, TJC, sex, age, alcohol consumption (g/day), smoking status, PtGA on a VAS, symptom duration (since first swollen joint), baseline mTSS. § Chi-square test. * Positive if > 50. † Positive if > 9 IU/ml. AUC: area under the curve; 25(OH)D: 25-hydroxy vitamin D2 and D3; ACPA: anticitrullinated protein antibodies; RF: rheumatoid factor; PtGA: patient's global assessment; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TJC: tender joint count.

other chronic rheumatic diseases[14,15]. However, the proportion of patients with vitamin D deficiency was lower in our study than in some other cohorts[16] and can be explained by the definition of insufficiency and deficiency, which can vary among countries.

Radiographic progression has rarely been considered in studies of the association of vitamin D and RA. Numerous studies have investigated the link between RA activity or disability and vitamin D levels[7,17]. An inverse correlation between serum vitamin D level and disease activity was reported in other cohorts of patients with established RA[7,8] or with early and treatment-naive RA[9] but not in an African American cohort of patients with recent-onset RA[13]. There are many discrepancies among these studies in terms of race, disease duration, vitamin D supplementation, and concomitant use of DMARD or biological treatments.

Another study did not find any association between low vitamin D serum level and radiographic progression in RA[8]. It was a posthoc analysis evaluating a tumor necrosis factor blocker in established RA, which suggests that the disease was more severe and that biologic use should have interfered with radiographic progression. Our data should also be regarded as exploratory, because the current analysis is an ancillary project conducted in the ESPOIR cohort.

In our study, vitamin D deficiency was an independent predictor of increased disability at 6 months. Low baseline vitamin D serum levels were associated with functional status in some other RA studies[17]. This low serum level may reflect a lack of sun exposure because of active disease and therefore more a consequence than a cause of the disability. We did not find any significant link between vitamin D and disability at 12 months, which could be explained by less effect of initial environmental factors on disability in the medium term.

This finding could suggest considering systematic routine dosage of 25(OH)D in early RA. However, it might also be assumed that low vitamin D rates are more a surrogate marker of global health impairment rather than a causal factor of the disease, which could explain the numerous negative results of vitamin D supplementation in various conditions where it was also suspected to play a central role[18]. Indeed, while supplementing vitamin D deficiency has shown benefit in the prevention of bone disease, the relevance of adding vitamin D to the current therapeutic strategy of early RA remains to be demonstrated. To date, trials of vitamin D replacement have shown conflicting results. A metaanalysis identified randomized trials that have investigated clinical effect of vitamin D supplementation for at least 3 months in rheumatic diseases, especially RA. After vitamin D supplementation, no statistically significant benefit was observed regarding patient's global VAS and DAS28[19].

Our study has some limitations. The number of patients among the groups was heterogeneous and results of some laboratory tests strongly associated with vitamin D, such as calcium or phosphorus tests, were not available for optimal analysis of vitamin D levels. In addition, some patients had a vitamin D supplementation at baseline but represented a very small proportion of the population. The strength of our study is that it concerns only early RA patients, which limits the bias of low vitamin D serum level linked to lack of sun exposure in patients with severe and established disease. Another strength is the use of a large prospective cohort of early arthritis patients from the community, who were naive of DMARD and glucocorticoid treatment.

Low serum vitamin D level at baseline among early RA patients was associated with more active and severe disease at baseline and may predict disability or radiographic progression over the first year. This finding reinforces the involvement of environmental factors in RA pathogenesis.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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