Association between Vitamin D deficiency and disease activity, disability and radiographic progression in early rheumatoid arthritis. The ESPOIR cohort.

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ABSTRACT

Objective: To evaluate the association of baseline serum level of vitamin D (vitD) 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. 25OH vitamin D2D3 level was measured at baseline. Baseline associations between vitD level and 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 vitD 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 RA patients were analyzed. VitD level was <10 ng/ml (deficiency, group 1), 10-30 ng/ml (low level, group 2) and ≥30 ng/ml (normal, group 3) for 114 (17.7%), 415 (64.6%), and 114 (17.7%) patients, respectively. At baseline, DAS28-ESR and HAQ-DI were higher with vitD deficiency as 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 vitD deficiency was associated with HAQ-DI at 6 months (OR=1.70) and mTSS at 12 months (OR=1.76).

Conclusion: VitD 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.

Competing Interests

The authors declare that they have no competing interests.

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Introduction

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 anti-citrullinated 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 (vitD) 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 recent studies underlined the possible link between low serum vitD level and high disease activity(7-9) or disability(10) in RA patients. We recently 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 vitD 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 25OH vitamin D2D3 level with disease activity measured by the disease activity score in 28 joints (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 25OH vitamin D2D3 level and functional disability or radiographic progression during the first year.

Methods

Study population

The ESPOIR cohort included 813 patients with early arthritis from 14 French rheumatology centres between 2002 and 2005(11) (ClinicalTrials.gov NCT03666091). Patients had two or more swollen joints for more than 6 weeks and less than 6 months. They should not have received disease-modifying anti-rheumatic drugs (DMARDs) 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 treatment as routine by their rheumatologist. Only patients who met the 2010 ACR/EULAR criteria for RA at baseline were selected for the 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 25OH vitamin D2D3 level was measured in the baseline blood sample from patients. Measurement involved an immunochemiluminescence assay (ng/ml; Roche-Cobas 8000, Roche, Switzerland) performed in a central laboratory (Biochemical Department, Lapeyronie Hospital, Montpellier, France). VitD level was considered normal at ≥30 ng/ml, insufficient at 10 to 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 global assessment on a 0-100 visual analog scale, erythrocyte sedimentation rate (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 Short Form 36 (SF36), socio-economic status evaluated by familial income. RF and ACPA (anti-CCP2)(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 vitD level and outcome measures (DAS28, HAQ-DI, mTSS) involved Pearson's 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. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. $P<0.05$ was considered statistically significant for variables in the multivariate model. SAS v9.4 was used for analysis.

Results

Patient characteristics

In total, 645 patients (79.34%) fulfilled the 2010 ACR/EULAR criteria for RA at baseline, and vitD 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 vitD supplementation at baseline, 6 and 12 months, respectively. HAQ-DI ≥0.5 at baseline, 6 and 12 months and radiographic progression at 12 months were similar for supplemented patients and the whole population (data not shown).

25OH Vitamin D2D3 analysis

Baseline mean (SD) serum vitD level was 20.55 (11.10) ng/ml. In total 114 (17.73%), 415 (64.54%) and 114 (17.73%) patients had baseline serum vitD level <10 ng/ml (deficiency, group 1), 10 to 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 these 2 groups for analysis. Baseline vitD distribution was bimodal and not Gaussian **(supplementary figure 1).** As expected, vitD supplementation was less frequent in group 1 than groups 2 and 3 at baseline (p=0.019). Proportion of patients with vitD 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 variables associated with vitD deficiency are presented in **Supplementary Table 1 and Supplementary Table 2.**

Disease activity

At baseline, mean (SD) DAS28 was higher with vitD 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, vitD 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 vitD 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, vitD 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 vitD 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, patient global assessment, physical component of SF36 and IgM-RF positivity **(Table 2)**. Socioeconomic status, assessed by familial income, was not selected as an independent variable in this model. VitD 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 vitD 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 vitD 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, VitD 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, patient global assessment and 25OH vitamin D2D3 deficiency were associated with radiographic outcome at 12 months". **(Table 3)**.

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 vitD 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 vitD was low, and most patients showed at least vitD insufficiency. At baseline, disease activity and functional and radiographic outcome were worsened with vitD deficiency. The secondary objective was to assess the link between vitD level and functional disability or radiographic progression during the first year. In addition to other known factors such as RF or ACPA, baseline vitD deficiency was an independent predictor of worse radiographic outcome at 12 months. VitD 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 vitD level and at least vitD insufficiency in most patients is globally consistent with findings in other RA cohorts(13) and in studies evaluating other chronic rheumatic diseases(14, 15). However, the proportion of patients with vitD 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 vitD and RA. Numerous studies have investigated the link between RA activity or disability and vitD levels(7, 17). An inverse correlation between serum vitD level and disease activity was reported in other cohorts of patients with established RA(7, 8) or with early and treatment naïve 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, vitD supplementation and concomitant use of DMARDS or biological treatments.

Another study did not find any association between low vitD serum level and radiographic progression in RA(8). It was a post-hoc 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 exploratory, since the current analysis is an ancillary project conducted in the ESPOIR cohort. In our

study, vitD deficiency was an independent predictor of increased disability at 6 months. Low baseline vitD serum levels were associated with functional status in some other RA studies(17). This low serum level may reflect a lack of sun exposure due to active disease and therefore more a consequence than a cause of the disability. We did not find any significant link between vitD 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 25OH vitamin D2D3 in early RA. However, it might also be assumed that low VitD 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 Vit D supplementation in various conditions where it was also suspected to play a central role(18). Indeed, while supplementing VitD deficiency has shown benefit in the prevention of bone disease, the relevance of adding VitD to the current therapeutic strategy of early RA remains to be demonstrated. To date, trials of VitD replacement have shown conflicting results. A recent meta-analysis identified randomized trials that have investigated clinical impact of VitD supplementation for at least 3 months in rheumatic diseases, especially RA. After VitD supplementation, no statistically significant benefit was observed regarding patient global visual analog scale and DAS28(19).

This study has some limitations. The number of patients among the groups was heterogeneous and results of some laboratory tests strongly associated with vitD, such as calcium or phosphorus tests, were not available for optimal analysis of vitD levels. In addition, some patients had a vitD 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 vitD 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 naïve of DMARDs and glucocorticoids treatment.

Conclusions

In summary, low serum vitD 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.

Ethics Approval and Consent to Participate

The protocol of the ESPOIR cohort was approved by the ethics committee of Montpellier, France (no. 020307, CNIL 02-1293), and all patients gave their signed informed consent before inclusion.

Authors' contributions

EG conceived of the study and drafted the manuscript, BC conceived of the study, and participated in its design and coordination and helped to draft the manuscript, NR performed the statistical analysis, CL participated in the design of the study, RS participated in the design of the study, FB participated in the design of the study, AMD performed the Vitamin D assessment, CD participated in the design of the study, JPD participated in the design of the study, GM conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Tables

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

Table 2: Logistic regression analysis of independent baseline variables associated with disability (Health Assessment Questionnaire Disability Index [HAQ-DI] score ≥0.5) at month 6.

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).

Supplementary material

Supplementary Table 1: Categorial baseline variables associated with vitamin D deficiency (<10ng/ml) (Univariate analysis).

Supplementary Table 2: Supplementary Table2. Quantitative baseline variables correlated with Vitamin D deficiency (<10ng/ml).

Supplementary Figure 1 Baseline distribution of levels of 25OH vitamin D2D3 in the ESPOIR cohort.

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

Female, n (%)	497 (77.05)
Age (years), mean (SD)	48.80 (12.22)
Caucasian, n (%)	592 (91.78)
Symptom duration at first visit (days), mean (SD)	102 (52)
25OH vitamin D2D3 level (ng/ml), mean (SD) (n=643)	20.55 (11.10)
25OH vitamin D2D3 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 level (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 (%) *Positive if >50 IU/ml*	314 (48.68)
IgM-RF positivity, n (%) *Positive if >9 IU/ml*	365 (56.59)
25OH vitamin D2D3 supplementation, n (%)	7 (1.09)

DAS28, Disease activity score in 28 joints; HAQ-DI, Health Assessment Questionnaire Disability Index; mTSS, van der Heijde-modified total Sharp score; HLA, human leukocyte antigen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ACPA, anti-citrullinated peptide antibodies; RF, rheumatoid factor; CCP, cyclic citrullinated peptide, IgM-RF, immunoglobulin M rheumatoid factor.

Table 2: Logistic regression analysis of independent baseline variables associated with disability (Health Assessment Questionnaire Disability Index [HAQ-DI] score ≥0.5) at month 6.

AUC=0.728	OR [95% CI]	P value§
25OH vitamin D2D3 level (ng/ml) *<10 versus ≥10*	1.70 [1.05-2.76]	0.031
Sex *(female vs male)*	1.74 [1.15-2.63]	0.008
Patient global assessment (VAS)	1.01 [1.00-1.02]	0.003
IgM-RF positivity (IU/ml) *Positive if >9*	0.63 [0.44-0.89]	0.009
Physical component of SF36	0.94 [0.92-0.96]	<0.001

§ chi-square test

*Baseline variables included in the model: 250H vitamin D2D3 level, sex, patient global assessment VAS, TJC, SJC, IgA-RF, IgM-RF, Physical component of SF36.

AUC, Area Under the Curve; OR, Odds Ratio; IC, Confidence Interval; TJC, tender joint count; SJC, swollen joint count; VAS, visual analog scale; IgA-RF, immunoglobulin A rheumatoid factor; IgM-RF, immunoglobulin M rheumatoid factor; SF36, Short Form 36.

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 value§**
25OH vitamin D2D3 level (ng/ml) *<10 versus ≥10*	1.76 [1.01-3.06]	0.045
ACPA positivity (IU/ml) *Positive if >50*	2.31 [1.32-4.03]	0.0032
IgA-RF positivity (IU/ml) *Positive if >9*	2.79 [1.56-4.98]	<0.001
Baseline mTSS	1.11 [1.07-1.14]	<0.001
Patient global assessment on a VAS	0.99 [0.98-0.998]	0.012

§ chi-square test

*Baseline variables included in the model: ACPA, IgM-RF, IgA-RF, ESR, CRP level, 25OH vitamin D2D3 level, TJC, sex, age, alcohol consumption (g/day), smoking status, patient global assessment on a VAS, symptom duration (since first swollen joint), baseline mTSS.

AUC, Area Under the Curve; OR, Odds Ratio; IC, Confidence Interval; TJC, tender joint count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ACPA, anti-citrullinated peptide antibodies; IgA-RF, immunoglobulin A rheumatoid factor; IgM-RF, immunoglobulin M rheumatoid factor; mTSS, van der Heijde-modified total Sharp score; VAS, visual analog scale.