Prevalence of vitamin D deficiency in rheumatoid arthritis and association with disease activity and cardiovascular risk factors: data from the COMEDRA study

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Abstract

Objective

The relationship between vitamin D and rheumatoid arthritis (RA) activity remains controversial. RA is a cardiovascular risk factor. A low level of vitamin D may increase blood pressure (BP) and decrease HDL-cholesterol.

We aimed to determine the prevalence of vitamin D deficiency in RA patients compared to controls, and also to investigate the relationship between vitamin D and RA activity, and between vitamin D and cardiovascular risk factors.

Methods

Patients in the COMEDRA study with established inactive RA (1987 ACR criteria) were matched with subjects from the NUTRINET-SANTE cohort (age, gender, latitude, sampling season). Vitamin D deficiency was defined as <10 ng/mL, and insufficiency as 10 to 29.9 ng/mL.

Results

Eight hundred and ninety-four RA patients were analysed, of which 861 were matched with controls. The prevalence of vitamin D insufficiency and deficiency was lower in RA patients than in controls: 480 (55.8%) vs. 508 (59%) and 31 (3.6%) vs. 45 (5.23%), respectively; p=0.04. There was an inverse correlation between vitamin D levels and RA activity assessed by DAS28-CRP (p=0.01), SDAI (p<0.001) and CDAI (p=0.001), but not DAS28-ESR after adjustment for age, gender, inclusion season, body mass index (BMI), vitamin D supplementation, disease duration, RF or anti-CCP status and RA treatments. Vitamin D levels were inversely correlated with BMI (p<0.001), but not with BP, total cholesterol, LDL-cholesterol, HDL-cholesterol or blood glucose.

Conclusion

This study demonstrates that vitamin D is inversely correlated with RA activity and BMI, but not with other cardiovascular risk factors.

Key words

rheumatoid arthritis, vitamin D, deficiency, prevalence, disease activity

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Introduction

Initially known for its effects on bone, vitamin D (VitD) has been extensively studied for its extra-osseous effects. Besides its well-demonstrated improvement in muscle function, VitD may also have a beneficial impact in areas as diverse as infections, cardiovascular diseases, and oncology (1). The immunomodulatory role of VitD has been much discussed in multiple sclerosis (MS), whose incidence is correlated with latitude, with an absence of MS in equatorial regions, and whose activity fluctuates according to the season (1). Furthermore, it has been shown that high levels of VitD or a diet rich in fish oil are inversely correlated with the onset of MS, and that there is an inverse association between levels of VitD and disease activity (1). An immunomodulatory role of VitD has also been documented in diabetes (1).

VitD has also been studied in autoimmune diseases: in systemic lupus erythematosus (SLE), epidemiological studies of VitD levels and SLE onset are conflicting (2). Similarly, studies are conflicting regarding SLE activity and VitD, some reporting an inverse correlation, and some not. Finally, if VitD supplementation significantly improves SLE fatigue, it does not improve SLE activity (2).

In rheumatoid arthritis (RA), it has been shown that VitD is involved in collagen-induced arthritis, where it may modulate the Th17 pathway (3). As in MS, the prevalence of RA increases with latitude; however, the prevalence of VitD deficiency is not different between RA and controls in the studies reported to date (4-6). The incidence of RA, meanwhile, is inversely correlated to the VitD level (7). In the meta-analysis by Song, patients with the highest total intake of VitD had a decreased relative risk (RR) of 24.2% (RR=0.758, 95% CI=0.577–0.937) for developing RA, compared to the group with the lowest intake (7). Numerous studies have evaluated the relationship between VitD and RA activity; the results are contradictory. Some have found an inverse relationship between VitD levels and RA activity, while others have not (4-6, 8-19).

RA leads to increased morbidity and mortality from cardiovascular disease compared to the general population (20), and RA is a cardiovascular risk factor as significant as diabetes (21). The traditional risk factors, in particular smoking, are increased in RA, but they alone do not explain the increased risk observed. In fact, after adjustment for the traditional cardiovascular risk factors, the relative risk of cardiovascular events is only very slightly diminished in RA (20). Interleukin-17 may be involved, since it results in endothelial dysfunction (22).

Vitamin D has been the subject of numerous studies in cardiovascular pathology, and in particular hypertension. In the general population, observational studies have shown an inverse relationship between VitD and hypertension (23). Mendelian randomisation genetic studies have also shown that each 10% increase in VitD concentration is associated with a significant decrease in diastolic blood pressure, non-significant decrease in systolic blood pressure, and a decreased risk of hypertension (24). In addition, VitD is associated with elevated levels of HDL-cholesterol (HDL-c), a protective factor in cardiovascular risk (25). In RA, it has been shown that VitD deficiency is associated with cardiovascular risk factors, with lower HDL-cholesterol, increased LDL-cholesterol and triglycerides, and a greater prevalence of metabolic syndrome and hypertension (26-28). A recent study from Delgado-Frías has, moreover, shown an association between endothelial function, as measured by brachial artery flow-mediated dilatation, and VitD levels in their control population, although it was not the case for their RA group (29).

The objectives of this study were to assess the prevalence of VitD deficiency in a large cohort of RA patients compared to a general population matched by sex, age and region of residence, and to study the relationship between VitD and RA activity on one hand, and cardiovascular risk factors on the other.

Materials and methods

Population

The COMEDRA study evaluated the

benefits of a nurse consultation on the management of comorbidities and patient self-assessment of RA activity (30). Collected for each patient at inclusion were: general characteristics (age, sex, body mass index [BMI]), RA disease duration and use of disease-modifying anti-rheumatic drugs (DMARDs); use of anti-inflammatory drugs (NSAIDs), current and in the last three months; cardiovascular risk factors (hypertension, diabetes, smoking, total cholesterol, HDL and LDL cholesterol, with calculation of the Framingham risk score); RA activity as assessed by DAS28-ESR (Disease Activity Score in 28 joints-erythrocyte sedimentation rate), DAS28-CRP (DAS28-C-reactive protein), SDAI (Simplified Disease Activity Index) and CDAI (Clinical Disease Activity Index), the modified HAQ (Health Assessment Questionnaire), the RAID score (Rheumatoid Arthritis Impact of Disease), laboratory parameters of inflammation (ESR, CRP), the presence of RA antibodies (rheumatoid factor [RF], anti-CCP [anti-cyclic citrullinated peptide]), and the VitD assay. Because of the pragmatic nature of the study, these assays were performed in individual centres. Each patient gave free and informed consent to participate and the study was approved by the French local authorities.

The control population was extracted from the NutriNet-Santé cohort, a study which began in France in 2009 and which aims to better assess the relationship between health and nutrition. This is a study in which voluntary subjects must complete online questionnaires, but those who wish may have a clinical and laboratory assessment, including a VitD assay.

Controls from this cohort were matched with COMEDRA patients by age, sex, sampling season for the VitD level and the region of residence.

Outcomes

The objectives of this study were to assess the prevalence of VitD deficiency in RA patients compared to the general population matched by sex, age and region of residence, and to study the relationship between VitD and RA activity on one hand, and cardiovascular risk factors on the other hand. A normal VitD level was defined as ≥30 ng/mL. Vitamin D levels were analysed in two ways: as a 3-class variable (deficiency if <10 ng/mL, insufficiency if 10–29.99 ng/mL and normal if ≥30 ng/mL) and then as a 2-class variable (deficiency-insufficiency if <30 ng/mL and normal if ≥30 ng/mL).

Statistical analysis

Statistical analysis was performed using Stata software (version 13, StataCorp, College Station, USA). The tests were two-sided, with a type I error set at α=0.05. Means and standard deviations (SD) or medians and interquartile ranges were presented for continuous variables, and numbers and associated percentages were calculated for categorical parameters. Comparisons of patients characteristics according to VitD levels considered as a 3-class variable were analysed using Chi-squared or Fisher's exact tests for categorical variables and ANOVA or Kruskal-Wallis test for quantitative variables (normality verified by the Shapiro-Wilk test and homoscedasticity by the Bartlett's test), followed if necessary by appropriate post-hoc multiple comparisons tests (Tukey-Kramer or Dunn, respectively). Comparisons considering VitD levels as a 2-class variable were analysed similarly, but using the Student's *t*-test or the Mann-Whitney test for quantitative variables (homoscedasticity verified by the Fisher-Snedecor test of equality of variances). A multivariate regression analysis with RA activity parameters as dependent variables (DAS28-CRP, SDAI, CDAI, tender joints) was performed, taking into account an adjustment on parameters considered significant in the univariate analyses and according to clinical relevance (5, 10, 26): age, gender, season, BMI and VitD supplementation. According to statistical distribution of dependent variables, multivariate linear regression was used for DAS28-CRP, Gamma regression for SDAI and CDAI, and Poisson regression for the number of tender joints. No imputation method was proposed, the rate of missing data being considered as negligible. Comparisons between cases and controls were performed according to recommendations using paired tests: Stuart Maxwell for categorical parameters (classes of VitD) and paired Student or Wilcoxon for quantitative variables.

Results

Nine hundred and seventy patients were included in the COMEDRA study between March and December 2011, but only 894 (79.3% female, mean age 58±11 years) had a VitD assay. Eight hundred and sixty-one controls from the NutriNet-Santé cohort were paired with 861 of these 894 patients, according to their sex, age, region of residence, and season in which the VitD assay was performed.

The characteristics of the RA population are presented in Table I.

The median value of VitD was 26.9 ng/mL [19.8 to 36.0] in the RA group, and 25.6 mg/L [18.6 to 34.0] in the control group. In the RA population, VitD was normal in 362 patients (40.5%); 501 patients (56.0%) had VitD insufficiency and 31 (3.5%) were deficient. Thirteen deficient patients, 206 patients with VitD insufficiency and 231 patients who had normal VitD levels were receiving supplementation, and this supplementation was significantly correlated with higher VitD levels (p<0.001). Data on VitD supplementation in the control population was not available. Compared to controls, RA patients had a lower prevalence of VitD insufficiency (RA: 480 (55.8%) *vs*. controls: 508 (59%)) and VitD deficiency (RA: 31 (3.6%) *vs*. controls: 45 (5.23%)) (p=0.04). Five hundred and eleven (59.3%) RA patients and 553 (64.2%) controls had below-normal VitD (p=0.03).

In the RA cohort, men had a higher frequency than women of VitD insufficiency or deficiency (125 (67.6%) *vs*. 407 (57.4%) respectively; p=0.01). There was no relationship between VitD and age. A relationship was found between VitD and seasons, with deficiency more common in winter and normal level in summer, when considering VitD as a 3-class variable (p=0.004). There was no difference in VitD levels, either in VitD insufficiency or deficiency, according to latitude (Table II). Mean concentrations were 27.6 ng/mL

Table I. Patient characteristics according to the Vitamin D level, taken as a 3-class variable (deficiency <10 ng/mL, insufficiency 10–29.99 ng/mL and normal ≥30 ng/mL) and as a 2-class variable (deficiency-insufficiency <30 ng/mL and normal ≥30 ng/mL).

	Total (n=894)	Deficiency (n=31)	Insufficiency (n=501)	Normal (n=362)	*p*-value (1)	*p*-value (2)
Patient characteristics						
Age in years, mean (SD)	58 (11)	57 (10)	57 (11)	59 (11)	0.05	0.01
Female, n (%)	709 (79.3)	23 (74.2)	384 (76.6)	302 (83.4)	0.04	0.01
BMI, mean (SD)	25.1 (4.8)	27.0 (6.4)	25.5 (4.9)	24.5 (4.4)	<0.001	<0.001
RF or positive anti-CCP, n (%)	747/890 (83.9)	25 (80.6)	429/499 (86.0)	293/360 (81.4)	0.17	0.09
Radiological erosions, n (%)	649/886 (73.3)	27 (87.1)	351/496 (70.8)	271/359 (75.5)	0.06	0.21
Length of RA duration, years, med [Q1 -Q3]	11.2 [6.3–19.1]	12.8 [6.0–18.6]	10.9 [5.9–18.4]	11.7 [6.7–20.3]	0.23	0.09
Corticosteroids in mg/day, med [Q1–Q3]	0.0 [0.0–5.0]	0.0 [0.0–5.0]	0.0 [0.0–5.0]	0.0 [0.0–4.0]	0.22	0.09
DMARD therapy						
Current DMARDs, n (%)						
None	14 (1.6)	0 (0.0)	7 (1.4)	7 (1.9)		
Synthetics only	250 (28.0)	11 (35.5)	137 (27.3)	102 (28.2)	0.85	0.86
Biologics only	155 (17.3)	3 (9.7)	92 (18.4)	60 (16.6)		
Synthetics and biologics	475 (53.1)	17 (54.8)	265 (52.9)	193 (53.3)		
Anti-TNF, n (%)	336 (37.6)	9 (29.0)	184 (36.7)	143 (39.5)	0.43	0.33
Tocilizumab, n (%)	133 (14.9)	8 (25.8)	88 (17.6)	37 (10.2)	0.002	0.001
Rituximab, n (%)	86 (9.6)	1 (3.2)	45 (9.0)	40 (11.0)	0.33	0.23
Abatacept, n (%)	72 (8.1)	1 (3.2)	38 (7.6)	33 (9.1)	0.55	0.34
Cardiovascular characteristics						
SBP (mm Hg), mean (SD)	124.9 (16.5)	122.1 (16.3)	124.8 (16.8)	125.2 (16.0)	0.58	0.61
DBP (mm Hg), mean (SD)	75.6 (11.4)	75.3 (10.6)	76.1 (11.2)	75.0 (11.7)	0.43	0.21
Total cholesterol (g/L), mean (SD)	2.2 (0.5)	2.2 (0.4)	2.2 (0.5)	2.1 (0.5)	0.45	0.23
HDL-cholesterol (g/L), mean (SD)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.30	0.13
LDL-cholesterol (g/L), mean (SD)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	0.72	0.47
Diabetes, n (%)	52 (5.8)	2 (6.5)	33 (6.6)	17 (4.7)	0.48	0.24
Current smoking, n (%)	147 (16.4)	5 (16.1)	80 (16.0)	62 (17.1)	0.90	0.65
Framingham score, med [Q1 -Q3]	7.0 [4.1–12.9]	7.7 [3.9–12.4]	7.1 [4.1–12.7]	6.9 [4.0–13.1]	0.88	0.61

(1): Vitamin D as a 3-class variable. (2): Vitamin D as a 2-class variable.
SD: standard deviation; BMI: body mass index; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide; RA: rheumatoid arthritis; med: median; Q1: 1st quartile: Q3: 3rd quartile; anti-TNF: Etanercept, Adalimumab, Infliximab, Certolizumab or Golimumab; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: highdensity lipoprotein; LDL: low-density lipoprotein.

(SD=13.6) for the Centre, 30.5 ng/mL (SD=17.6) for the North, and 29.2 ng/mL (SD=15.3) for the South (p=0.10; data not shown). Also, there was no North-South gradient for RA activity assessed by DAS28-ESR, DAS28CRP, SDAI and CDAI (data not shown).

In univariate analysis, there was an inverse correlation between VitD and disease activity assessed by DAS28-CRP, SDAI, and CDAI, but not DAS28-ESR. Among the DAS28 parameters, only an inverse relationship between VitD and the number of tender joints was found, but only considering VitD as a binary variable. There was also an inverse correlation with BMI and treatment with tocilizumab, whether VitD was considered in 2 or 3 classes. After adjustment for age, sex, season of inclusion and BMI and VitD supplementation, an inverse correlation persisted between VitD and RA activity assessed by SDAI and CDAI, whether VitD was considered in 2 or 3 classes, and DAS28-CRP, and the number of tender joints when considering VitD in 2 classes (Table III). These results were not changed if they were further adjusted in the multivariate model for disease duration, immunologic status (RF or anti-CCP), and treatment with tocilizumab and other RA treatments (results not shown).

No association was found between VitD and cardiovascular risk factors, apart from BMI, be it blood pressure, total cholesterol and its sub-fractions, or overall cardiovascular risk as assessed by the Framingham equation (Table I).

Discussion

Our study shows an inverse relationship between levels of VitD and RA activity, assessed by DAS28-CRP, SDAI and CDAI, but not DAS28-ESR. VitD deficiency or insufficiency seems however less frequent in our RA patients than in the general population. We did not find a relationship between latitude and VitD deficiency in RA patients, as has been found in numerous studies on the French population (31). This could be explained by greater physician awareness in higher latitudes of the need for increased supplementation due to decreased sunshine.

Considering VitD as either normal or abnormal, we also found an inverse relationship between VitD and the number of tender joints.

Our results are in accord with those of Cutolo and Rossini (4-5). Rossini found a similar prevalence of VitD deficit (<20 ng/mL) compared to controls. Thus, 55% of 1,191 consecutive RA patients received no VitD supplement, and a deficit was present in 51.8% of them, while a deficit was present in 58.7% of controls who were not receiving supplements (5). In our study, 438 patients with RA (49%) were not supplemented, and insufficiency or deficiency was pre-

Table II. Prevalence of vitamin D deficiency/insufficiency by sex, age, season and region.

	Deficiency (n=31)	Insufficiency (n=501)	Normal (n=362)	Deficiency/ Insufficiency/ Normal *p*-value	Deficiency – Insufficiency/ Normal *p*-value
Gender					
Female (n=709)	23 (3.2)	384 (54.2)	302 (42.6)	0.04	0.01
Age					
18-29 years (n=16)	0 (0.0)	12 (75.0)	4 (25.0)		
30-39 years (n=33)	0 (0.0)	19 (57.6)	14 (42.4)		
40-49 years (n=151)	9 (5.9)	88 (58.3)	54 (35.8)	0.08	0.05
50-59 years (n=273)	8 (2.9)	168 (61.6)	97 (35.5)		
60-69 years (n=284)	11 (3.9)	141 (49.6)	132 (46.5)		
70-80 years (n=137)	3 (2.2)	73 (53.3)	61 (44.5)		
*Season**					
Spring (n=408)	21 (5.1)	241 (59.1)	146 (35.8)		
Summer (n=301)	4 (1.3)	160 (53.2)	137 (45.5)	0.004	0.06
Autumn (n=160)	3 (1.9)	88 (55.0)	69 (43.1)		
Winter (n=25)	3 (12.0)	12 (48.0)	10 (40.0)		
*Region***					
Centre (n=307)	10 (3.3)	186 (60.6)	111 (36.1)	0.39	0.16
North (n=442)	15 (3.4)	238 (53.8)	189 (42.8)		
South (n=145)	6 (4.1)	77 (53.1)	62 (42.8)		

*Inclusion season: all inclusions were made in 2011 (From January 1st to March 19 – Winter; from March 20 to June 20 – Spring; from June 21 to September 22 – Summer; from September 23 to December 21 – Autumn; from December 22 to 31 – Winter).
**Region: North: Brest, Le Mans, Lille, Nancy, Paris, Strasbourg, Rennes and Rouen; Centre: Bordeaux, Clermont-Ferrand, Grenoble and Lyon; South: Marseille, Nice and Toulouse.

sent in 309 (70.5%) of them. The difference between our results and those of Rossini, however, can at least partially be explained by a difference in cut-off, since we defined VitD insufficiency as <30 ng/mL, and Rossini as <20 ng/mL. Rossini found an inverse relationship in RA patients not taking VitD supplements between the VitD level and the DAS28 and HAQ, which persisted after adjustment for body mass index and sun exposure (5). This correlation was confirmed by a subanalysis of this study on 581 patients divided among South, North and Central Italy, with higher disease activity in the South, where VitD levels were the lowest, presumably because of higher BMI and lower sun exposure (6). Cutolo studied the levels of VitD in a population of Italian and Estonian RA patients (4). While there were no differences between RA patients and controls concerning VitD insufficiency, lower levels of VitD were observed in Estonian patients. An inverse correlation between VitD levels and disease activity assessed by DAS28 was found in summer in Italian patients and in winter in Estonian patients (4). In our study, we did not find any North-South gradient for the levels of VitD or disease activity.

In established RA, several other studies have found an inverse correlation between VitD levels and disease activity (9-14). Depending on the studies, an inverse correlation was found between VitD levels and the DAS28, VAS (Visual Analogue Scale) for pain, the number of tender and swollen joints, inflammatory markers (ESR and/or CRP) VAS for fatigue, morning stiffness and the HAQ (11-12). In addition to clinical parameters and ESR, Hong also found, after adjusting for sex, age and BMI, an inverse association between VitD and serum levels of interleukins 17 and 23 (13). The same findings were made in early RA; Patel found an inverse relationship between VitD levels and the number of tender joints, the DAS28 and the HAQ (9). Similar data were found by Zakeri and Craig, who respectively studied 66 and 266 patients with early RA. However, in Craig's study, the inverse relationship between VitD and pain, the number of synovitis and the DAS28 no longer remained after adjustment for age, sex and season (9, 14). The studies are however not unanimous. Nine studies involving a total of 1,249 patients found no relationship between VitD and RA activity (15-19).

Unlike the other studies, the only inverse correlation we found between the DAS28 parameters and VitD levels was with the number of tender joints when considering VitD as normal or abnormal. It is possible that this can be explained by the analgesic effect of VitD, which has been suggested by some authors (32). In our study, the absence of correlation with the number of swollen joints does not support the hypothesis of an immunomodulatory role of VitD. However, the inverse relationship between VitD and RA activity does not prove its hypothetical aetiological role in RA activity. This could be explained by the fact that patients with the most pain who are functionally disabled are unable to expose themselves to the sun as much as patients with less pain, and therefore have lower levels of VitD because of a synthesis deficiency, even if sun exposure was taken into account in the Italian case-controlled study (5).

In contrast to the study of American veterans who, after adjustment for age, sex and season, had shown an association between VitD insufficiency/deficiency and the presence of anti-CCP (8), or the CARMA study, where a marginally significant association between VitD insufficiency/deficiency and ACPA positivity was found (adj. OR=1.45; 95% CI=0.99–2.12; p=0.056) (33), we did not find a relationship between VitD levels and the seropositivity or the erosive character of RA. Neither we found an association with cardiovascular risk factors, be it systolic or diastolic blood pressure, lipid assessment parameters, or cardiovascular risk factors expressed by a risk equation. Yet, it has been clearly demonstrated that there is an inverse relationship between VitD levels and blood pressure in both general population and RA patients (23, 26).

As in other studies on VitD in the general population or in RA patients, we have shown that its level is inversely correlated with BMI, which is also a predictive factor of the VitD level in Rossini's study, as is sun exposure (5). This relationship is known, and is due

Table III. Associations in univariate and multivariate analyses between RA activity parameters and vitamin D considered as a 3-class variable (deficiency: <10 ng/mL; insufficiency: 10–29.99 ng/mL; normal: ≥30 ng/mL) and in 2 class (deficiency-insufficiency: <30 ng/mL; normal: ≥30 ng/mL).

	Total (n=894)	Deficiency (n=31)	Insufficiency (n=501)	Normal (n=362)	VitD in 3 classes		VitD in 2 classes	
					Unadjusted model	Adjusted model	Unadjusted model	Adjusted model
					p-value	*p*-value	*p*-value	*p*-value
DAS28-ESR, mean (SD)	3.0 (1.3)	3.4 (1.3)	3.1 (1.3)	3.0 (1.2)	0.08	I: 0.06	0.08	
DAS28-CRP, mean (SD)	2.8 (1.1)	3.2 (1.2)	2.9 (1.1)	2.7 (1.1)	0.02	D: 0.05	0.02	0.04
SDAI, mean (SD)	10.9 (8.8)	13.6 (10.0)	11.5 (9.4)	10.0 (7.6)	0.05	I: 0.01	0.03	0.006
med [Q1– Q3]	9.1 [4.6–15.1]	10.1 [6.9–19.6]	9.3 [5.0–15.2]	8.5 [4.0–14.3]		D: 0.03		
CDAI, mean (SD)	10.4 (8.5)	12.9 (9.7)	10.9 (8.9)	9.5 (7.6)	0.05	I: 0.02	0.03	0.01
med [Q1– Q3]	9.0 [4.0–14.0]	10.0 [6.5–18.5]	9.0 [5.0–15.0]	8.0 [3.0–14.0]		D: 0.04		
mHAQ, mean (SD)	0.39 (0.45)	0.42 (0.63)	0.39 (0.46)	0.39 (0.43)	0.86		0.66	
med [Q1– Q3]	0.25 [0.00–0.63]	0.25 [0.00–0.50]	0.25 [0.00–0.63]	0.25 [0.00–0.63]				
RAID, mean (SD)	2.9 (2.0)	3.3 (2.1)	3.0 (2.1)	2.8 (2.0)	0.17		0.08	
med [Q1– Q3]	2.7 [1.3–4.3]	3.1 [1.8–4.5]	2.8 [1.4–4.4]	2.5 [1.2–4.0]				
ESR (mm/h), med [Q1– Q3]	10.0 [5.0– 20.0]	11.0 [6.5–22.5]	10.0 [5.0–19.0]	10.0 [5.3– 19.8]	0.44		0.51	
CRP (mg/L), med med [Q1– Q3]	1.9 [0.0–5.7]	3.4 [1.0–7.3]	1.9 [0.0–5.7]	2.0 [0.3–5.3]	0.18		0.55	
NSJ (0-28), med [Q1– Q3]	1.0 [0.0–3.0]	1.0 [0.0–5.5]	1.0 [0.0– 3.0]	1.0 [0.0–3.0]	0.16		0.15	
NTJ (0-28), med [Q1– Q3]	2.0 [0.0–5.0]	2.0 [1.0–3.5]	2.0 [0.0–5.0]	1.0 [0.0–4.0]	0.06		0.02	0.04
Patient global assessment (0-10), med [Q1–Q3]	3.0 [1.0–4.0]	3.0 [2.0–5.0]	3.0 [1.0–4.0]	2.0 [1.0–4.0]	0.21		0.15	

VitD: vitamin D; DAS28-ESR: Disease Activity Score 28 joints, using the ESR; SD: standard deviation; DAS28-CRP: Disease Activity Score 28 joints, using the CRP; SDAI: Simple Disease Activity Index; med: median; Q1: 1st quartile; Q3: 3rd quartile; CDAI: Clinical Disease Activity Index; mHAQ: Modified Health Assessment Questionnaire; RAID: Rheumatoid Arthritis Impact of Disease; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; NSJ: Number of swollen joints; NTJ: Number of tender joints; I: Insufficiency; D: Deficiency.
Adjusted model: adjusted for age, sex, season of inclusion/of assay, body mass index and vitamin D supplementation.

to VitD storage in adipocytes (34). This could possibly explain why in our study there was also an inverse correlation with tocilizumab, which can cause an increase in abdominal fat, sometimes with the onset of metabolic syndrome. However, the data for interleukin 6 and VitD suggest rather an inverse correlation between these two parameters (35). Our results in the analysis of the association between VitD and RA activity remained significant after adjustment for the confounding factors usually found; age, sex, inclusion season, BMI and VitD supplementation. They were also significant when adjusted for the antibody status of RA, duration of the disease, treatment with tocilizumab and/or other treatments for RA.

If this study is characterised by its strong power, it has several biases. The first is a selection bias, as evidenced by the percentage of supplemented patients (50.3%), and by lower levels of VitD deficiency/insufficiency than those reported in the literature, since only 56% of our RA patients had VitD insufficiency and 3.5% deficiency. It is difficult to compare our results to all of the data in the literature, as the cut-offs to define VitD insufficiency and deficiency vary depending on the studies. Using our cut-offs, a deficiency is present in 11.5% of 4,793 patients in a Japanese series (36), and insufficiency in 84% of the American veterans analysed by Kerr (8). There is also a probable selection bias in the control population. This was indeed a population of volunteers enrolled in an online study promoting research and the benefits of nutrition for health. It is therefore no exaggeration to think that this population is probably more interested in, and therefore attentive to their health and the nutritional aspects of food, with the possibility of vitamin supplement use, including VitD, sold without prescription in drugstores or supermarkets. This, however, would result in an overestimation of VitD levels in this population, which nevertheless appear lower than in RA patients, and the same bias could be discussed for RA patients who accepted to be included in the COMEDRA study.

As we said earlier, the association between VitD deficiency and RA activity does not allow conclusions as to which is the cause and which is the effect. In animals, it has been shown that 1-alpha-OH-D3 reduces the incidence and severity of collagen-induced arthritis (37). In humans, three previous clinical trials with small numbers of patients have been performed with 1-alpha-OH-D3; the results are contradictory, since Andjelkovic showed a good efficacy of α-calcidiol (38), Yamauchi a moderate but not significant improvement (39), and Hein no significant decrease in the number of tender or swollen joints or improvement in inflammation parameters (ESR, CRP) (40). The benefits of VitD in extraosseous manifestations is

thus strongly questioned (41), and can only be demonstrated by a randomised, placebo-controlled trial, currently ongoing (42).

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