Vitamin D status in spondyloarthritis: results of the ASAS-COMOSPA international study

S. Fernandes[1,2], A. Etcheto[1,3], D. van der Heijde[4], R. Landewé[5], F. van den Bosch[6], M. Dougados[1,3], A. Moltó[1,3]

[1]Paris Descartes University, Rheumatology Department, Cochin Hospital, AP-HP, Paris, France; [2]Rheumatology and Metabolic Bone Diseases Department, Santa Maria Hospital, CHLN, Lisbon Academic Medical Centre, Lisbon, Portugal; [3]INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France; [4]LUMC, Leiden, The Netherlands; [5]ARC, Amsterdam and Zuyderland Hospital Heerlen, Heerlen, The Netherlands; [6]Ghent University Hospital, Ghent, Belgium.

Abstract

Objective

SpA encompasses both bone production and bone loss, and the latter is particularly linked to inflammation. Vitamin D deficiency has been associated with several inflammatory conditions (i.e. cardiovascular disease, rheumatoid arthritis), but it has been poorly evaluated in SpA patients.

We aimed to a) describe the prevalence of vitamin D deficiency in SpA patients worldwide; b) compare SpA patients with and without vitamin D deficiency in terms of disease phenotype, activity severity and comorbidities.

Methods

This is an ancillary study of the ASAS-COMOSPA study initiative, an international cross-sectional study of patients with SpA. Demographics, patients' phenotype, disease activity/severity measures and comorbidities were assessed. Serum 25-hydroxyvitamin D (25OHD) deficiency was defined as <20 ng/mL (<50 nmol/L). Statistical analysis: a) prevalence of vitamin D deficiency; b) comparison of the disease presentation/activity/severity and comorbidities in the group of patients with and without vitamin D deficiency by bi-variable and multivariable analysis.

Results

Vitamin D deficiency was observed in 527(51.2%) of the 1030 patients with available data who were not receiving any supplementation. Vitamin D deficiency was independently associated with the presence of radiographic sacroiliitis (OR=2.1 [95%CI1.3; 3.3]) and a 25OHD measured in winter and in spring (OR=1.88 [95%CI 1.2; 2.9]).

No independent association between vitamin D deficiency and comorbidities was found.

Conclusion

This study suggests that vitamin D deficiency is common in SpA worldwide and is associated with season but also with more severe forms of SpA.

Key words

vitamin D deficiency, spondyloarthritis, comorbidities

Sílvia Fernandes, MD, MSc
Adrien Etcheto, MSc
Désirée van der Heijde, MD, PhD
Robert Landewé, MD, PhD
Filip van den Bosch, MD, PhD
Maxime Dougados, MD
Anna Moltó, MD, PhD

Please address correspondence to:
Dr Sílvia Fernandes,
Department of Rheumatology and Metabolic Bone Diseases,
Santa Maria Hospital, CHLN,
Lisbon Academic Medical Centre,
Avenida Prof. Egas Moniz,
1649-035 Lisbon, Portugal.
E-mail: silvia_tfernandes@yahoo.com

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Introduction

Spondyloarthritis (SpA) is a prevalent chronic inflammatory rheumatic disease. Clinical presentation of SpA may include back pain, oligoarthritis, dactylitis, enthesitis, and organ-specific extraskeletal manifestations such as uveitis, inflammatory bowel disease (IBD) and psoriasis. New bone formation (*i.e.* growth of bony spurs along the intervertebral spaces (syndesmophytes) and sacroiliac joints) is one of the hallmarks of axial SpA, particularly in long-standing disease (1), but axSpA is paradoxically associated with low bone mineral density (2, 3). It was classically thought that immobilisation and movement restriction due to spine involvement were the main causative factors for osteoporosis in SpA, but recent studies have reported the presence of significant bone loss already in early stages of the disease, when ankylosis is absent, and particularly associated with inflammatory activity (4).

Vitamin D is known for its homeostatic actions on serum calcium levels but may also exert other effects. Vitamin D deficiency has been associated with inflammatory diseases (*e.g.* cardiovascular diseases, cancer but also rheumatic diseases) and all-cause mortality (5) and it has been suggested that this association could be related to the immune-modulating effects of vitamin D (6). Furthermore, vitamin D has been associated with disease activity (7) and severity in rheumatoid arthritis (8).

Surprisingly, only few studies have evaluated the association between vitamin D levels and disease activity and severity in SpA and the results are conflicting (9, 10). To the authors best knowledge the association between vitamin D deficiency and comorbidities in patients with SpA has not yet been studied.

These remarks prompted us to explore the world-wide ASAS-COMOSPA study (Assessment in SpondyloArthritis international Society – COMOrbidities in SPondyloArthritis) (11) to evaluate whether SpA patients that are deficient in vitamin D presented with other disease-manifestation and comorbidities than SpA patients that are not deficient in vitamin D.

Methods

Study population

The present work is an ancillary study of the ASAS-COMOSPA study. Briefly, the ASAS-COMOSPA study is an observational, cross-sectional, multicentre, world-wide study, conducted in 22 countries representing 4 continents (Africa, America, Asia and Europe), aiming to assess the prevalence of comorbidities and risk factors for comorbidities in different countries and to evaluate the level of implementation of the current recommendations to prevent/manage comorbidities. Consecutive patients over 18 years, classyfing as SpA (axial or peripheral) according to the ASAS criteria (12), were included in the ASAS-COMOSPA study (11). All patients signed informed consent.

Data collected in the ASAS-COMOSPA study

The data collected in the ASAS-COMOSPA study have been reported elsewhere (11). Briefly, data comprised different chapters: 1) demographics (*e.g.* age, gender, country); 2) disease data (*e.g.* disease duration, axial/peripheral/enthesitic involvement, Ankylosing Spondylitis Disease Activity Score C-reactive protein (ASDAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), past and current SpA treatments, and 3) specific co-morbidities: osteoporosis, infections, cancer and cardiovascular and gastrointestinal diseases.

Serum 25-hydroxyvitamin D (25(OH) D) deficiency was defined as a plasma level below 20 ng/mL (<50 nmol/L) of available data. No central determination was performed, and the method of assay used to determine the level of 25HOD was not specified for each centre.

Statistical analysis

The statistical analysis was performed on the ASAS-COMOSPA study database locked on November 30th, 2014.

Since vitamin D supplementation might interfere with the evaluation of the impact of vitamin D deficiency in disease activity/severity and comorbidities, we decided to exclude patients who were receiving vitamin D supplementation from our analysis.

No blood test was performed during the ASAS-COMOSPA study. Current Vitamin D plasma levels were collected from the medical file of the patients included in the study, when available.

In order to avoid a multiple testing bias and to aggregate a large number of comorbidities into one variable, we computed a multi-morbidity index, based on the previous work of Radner *et al*. (13) which has been validated in the COMORA study (a cross sectional study on comorbidities in RA, in which comorbidities had been collected similarly as in the ASAS-COMOSPA study) (14). We used the simple count multi-morbidity index described in the original manuscript (*i.e*. one point per comorbidity, ranging from 0 to 12). The included comorbidities are detailed in Supplementary Table I, but with the deliberate exclusion of psoriasis and inflammatory bowel disease of the Index, since these conditions were considered extra-articular manifestations rather than co-morbidities in patients with SpA.

Patients with/without vitamin D deficiency were compared in terms of disease presentation activity/severity and the multi-morbidity index first by bi-variable analysis (Chi-square and Student *t*-tests if appropriate); thereafter, a logistic regression (with vitamin D deficiency (yes *vs*. no) as the binary dependent variable) was performed, including in the model age and gender by default, as well as those other variables that showed differences between the absence and presence of Vitamin D deficiency at a *p*-value <0.10 in the bivariate analysis. All statistical analyses were performed with SAS v. 9.3.

Results

Of the 3984 patients in the ASAS-COMOSPA study, 3131 were not receiving any vitamin D supplementation, and among them, 1030 patients from 18 of the 22 participating countries (*i.e*. Belgium, France, Portugal, Germany, Netherlands, Spain, Russia, UK, Morocco, Egypt, USA, Canada, Turkey, Argentina, China, South Korea, Singapore, and Taiwan) had data available on vitamin D and were included in our analysis (Fig. 1).

Prevalence of vitamin D deficiency in our sample was 51.2% (527/1030 patients).

Patients with vitamin D deficiency had higher mean (SD) BMI (26.3 (5.3) *vs*. 25.7 (5.3), *p*=0.02) and were more frequently living above the 37° parallel (53.0% *vs*. 47.0%, respectively; *p*<0.01). As expected, vitamin D deficiency was more frequently observed when measurements were performed in winter/spring *vs*. summer/fall (56.8% *vs*. 43.2%, respectively, *p*<0.01) (Table I).

There were no differences concerning disease phenotype, and surprisingly there were fewer patients with IBD in the group of patients with vitamin D deficiency. Interestingly, patients with vitamin D deficiency presented with higher disease activity, measured by the ASDAS (3.0 (1.3) *vs*. 2.7 (1.2); *p*<0.01) and the BASDAI (3.9 (2.3) *vs*. 3.5 (2.3); *p*=0.01), although the observed differences were small.

Patients deficient in 25OHD were more likely to have radiographic sacroiliits (80.5% *vs*. 66.2%; *p*<0.01) and hip articular replacement (4.2% *vs*. 1.2%, *p*<0.01) than patients without vitamin D deficiency. The number of patients with a bamboo spine and the multimorbidity index were slightly higher in the group of patients with vitamin D deficiency (5.3% *vs*. 3.6% and 0.94 (1.04) *vs*. 0.87 (0.98), respectively), but these differences did not reach a statistical significance. No differences were observed with regard to the treatments received. (Table I)

In the multivariable analysis, only season (winter/spring) (OR 1.9 [95%CI=1.2; 2.9]) and the presence of radiographic sacroiliitis (OR 2.1 [95%CI=1.3; 3.3]) remained independently associated with vitamin D deficiency.

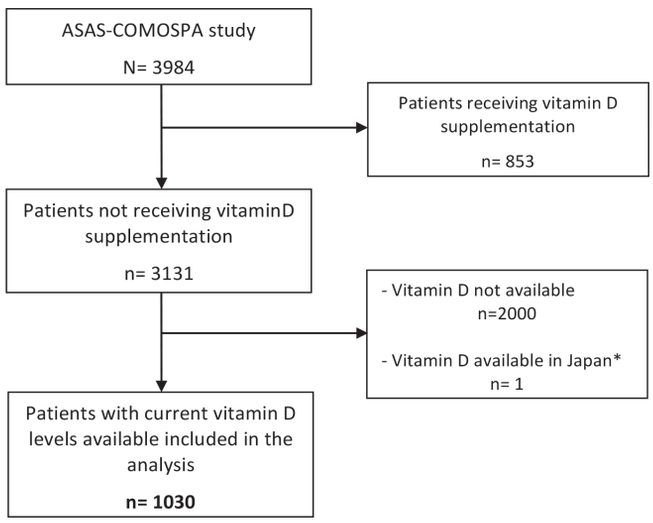

Fig. 1. Flow chart of the study.
*We decided to exclude Japan from the analysis since only 1/161 patients had a vitamin D available.

Discussion

This is the first worldwide study providing data regarding the vitamin D status in SpA patients.

Vitamin D deficiency prevalence was 51.2% in our patients sample. Indeed, the prevalence of vitamin D deficiency in SpA has been reported to range from 29.3% to 51.0% (15-17). It is worth noting that including only patients with available data on vitamin D levels and without any vitamin D supplementation in the analysis might have led to selection (chanelling bias): *i.e*. over-estimation of the vitamin D prevalence, as only patients in whom the physicians suspected a vitamin D deficiency had their vitamin D level determined. However, even assuming that all patients without a vitamin D level were not deficient and that all patients with vitamin D supplementation were deficient at some point, the prevalence would still be over 30% (data not shown). Furthermore, it is worth noting that we did not find major differences in the patients with and without missing data on vitamin D (data not shown).

Vitamin D levels have been reported to change over the seasons, with peak levels of vitamin D usually occurring in late summer, and the lowest values at the beginning of spring (18). However,

Table I. Patients and disease characteristics with regard to vitamin D deficiency in SpA patients.

Characteristics	All patients with available data on vitamin D n=1030	Vitamin D deficiency		*p*-value
		YES n=527	NO n=503	
Age (years), (n=1017)*	42.4 ± 13.6	41.7 ± 13.4	43.1 ± 13.8	0.08
Gender female (n=1030)	322 (31.3)	168 (31.9)	154 (30.6)	NS
BMI (kg/m^2), (n=1024)	26.0 ± 5.3	26.3 ± 5.3	25.7 ± 5.3	0.02
Latitudes above 37° North (n=1030)	848 (82.3)	450 (53.0)	398 (47.0)	0.01
Winter and Spring (n=1027)	570 (55.5)	324 (56.8)	246 (43.2)	<0.01
Disease phenotype				
Axial involvement (n=1030)	911 (88.5)	475 (90.1)	436 (86.7)	NS
Peripheral articular disease (n=1029)	647 (62.9)	337 (64.1)	310 (61.6)	NS
IBD (n=1030)	53 (5.2)	23 (4.4)	30 (6.0)	NS
Psoriasis (n=1030)	239 (23.2)	122 (23.1)	117 (23.3)	NS
X-ray sacroiliitis (n=944)	694 (73.5)	388 (80.5)	306 (66.2)	<0.01
MRI sacroiliitis (n=608)	440 (72.4)	237 (75.5)	203 (69.0)	NS
Disease activity				
ASDAS CRP, (n=1024)	2.11 ± 1.1	3.0 ± 1.3	2.7 ± 1.2	0.01
BASDAI, (n=1027)	3.7 ± 2.3	3.9 ± 2.3	3.5 ± 2.3	0.01
CRP (mg/dL), (n=1021)	0.6 ± 1.1	0.6 ± 1.1	0.5 ± 1.2	NS
Disease severity and function				
Hip articular replacement (n=1030)	28 (2.7)	22 (4.2)	6 (1.2)	0.01
Bamboo spine (n=1028)	46 (4.5)	28 (5.3)	18 (3.6)	NS
BASFI, (n=1024)	3.0 ±2.6	3.1 ±2.7	2.8 ±2.5	NS
Treatments				
NSAID ever (n=1030)	919 (89.2)	479 (90.9)	440 (87.5)	NS
DMARDs ever (n=1030)	814 (79.0)	428 (81.2)	386 (76.7)	NS
TNF alpha-b ever (n=1030)	499 (48.5)	254 (48.2)	245 (48.7)	NS
Multimorbidity index (n=1030)	0.91 ±1.01	0.94 ±1.04	0.87 ±0.98	NS

*All results are presented as mean ± standard deviation and number (percentage) for continuous and categorical variables, respectively.
BMI: Body Mass Index; IBD: Inflammatory bowel disease; MRI: magnetic resonance imaging; BASFI: Bath Ankylosing Spondylitis Functional Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; DMARDs: disease-modifying anti-rheumatic drugs; NSAID: non-steroidal anti-inflammatory drugs; TNF alpha b: tumour necrosis factor alpha blockers.

Supplementary Table I. List of comorbidities included in the multimorbidity index adapted from Radner *et al*.[1]

Diverticulitis
Hypertension
Cancer (any)
Diabetes
Osteoporosis
Coronary heart disease
Stroke/Transient ischaemic attack
Chronic Kidney Disease
Obesity
Alcohol problems
Chronic Obstructive Pulmonary disease
Hepatitis (viral)

[1]Radner H, Yoshida K, Mjaavatten MD *et al*.: Development of a multimorbidity index: Impact on quality of life using a rheumatoid arthritis cohort. *Semin Arthritis Rheum* 2015; 45: 167-173.

to date, published data on vitamin D status in SpA failed to document this association with season (9, 19). This is to our knowledge the first study confirming such an association in SpA patients. Interestingly, in our study, patients with vitamin D deficiency were more likely to have undergone the blood test in winter and spring (*i.e*. during and right after the less sunny season of the year), however the association with the season remained after full adjustment. Also in the context of greater sunny exposure, and as reported in previous studies, patients with vitamin D deficiency were more frequently living in latitudes above 37°; however, this association was not retained in the multivariable analysis.

Patients with vitamin D deficiency had higher disease activity parameters, but we did not find any difference in terms of local inflammation (*i.e*. MRI sacroiliitis) in patients with/without vitamin D deficiency. In terms of disease severity, patients with vitamin D deficiency had more severe disease (*i.e*. more radiographic sacroiliitis and more hip replacements). However, the multivariable regression only retained the presence of radiographic sacroiliitis as independently associated with vitamin D deficiency. Structural damage of the sacroiliac joints usually does not cause functional impairment nor mobility limitations *per se*, but patients with radiographic sacroiliitis present more frequently with structural damage of the spine. This damage might contribute to mobility limitation and inability to exercise and potentially decreased outdoor activity and sun exposure. Indeed, the presence of a bamboo spine was more frequent in the group of patients with vitamin D deficiency, although this difference was not statistically significant. Here again, selection may play a role: patients with more severe disease will more frequently see their rheumatologists and would more likely be prescribed with a 25HOD dosage. However, as mentioned above, we did not find major differences in disease presentation/activity/severity in patients with and without vitamin D data available (data not shown).

Another limitation of this analysis, is the lack of information on vitamin D intake from food, physical impairment, and from frequency/amount of sunlight exposure. Also other variables like skin colour and individual life style (*e.g*. diet) were not assessed. Finally, 25HOD determination was not centralised, and values of serum levels derived from a variety of laboratory methods used in different countries.

The strengths of this study are related to both the size of the sample and the multi-centric worldwide design of the study, including more than 1000 patients from 18 countries world-wide. Furthermore, the extent of the collected data allowed us to control for many important confounding factors regarding vitamin D deficiency, despite the potential selection biases.

Our study suggests that vitamin D deficiency in SpA seems to be prevalent worldwide. This deficiency is more often observed during less sunny seasons of the year, and in patients with more severe forms of axial SpA. Further studies with systematic dosage of 25HOD levels in SpA patients could lead to confirmation of our findings.

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