# Vitamin D, disease activity and comorbidities in early spondyloarthritis

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## Abstract

### Objective

*To assess the vitamin D status in patients presenting inflammatory back pain suggestive of axial spondyloarthritis and to assess the relationship between vitamin D status and disease activity/severity; comorbidities at baseline and during the first two years of follow-up.*

### Methods

*DESIR is a prospective, multicentre, observational study. Vitamin D deficiency was defined as <50 nmol/L and severe deficiency less than 25 nmol/L. Clinical variables were collected at each six month interval visits during the two-year follow-up.*

### Results

*A total of 700 patients were analysed. The mean vitamin D was 54.2±28.7 nmol/L. Severe deficiency were observed in 11.7% versus 5% in the DESIR cohort versus the French population respectively. In the DESIR cohort, after adjusting for season and ethnicity, vitamin D deficiency remained significantly associated with presence of radiological sacroiliitis, higher ASDAS score and elevated BASDAI. Such association was also found between vitamin D deficiency and the mean value of disease activity/severity parameters during the two-year follow-up. Otherwise, vitamin D deficiency was significantly associated with the presence of baseline abdominal obesity (OR=1.65 [1.05–2.61], p=0.03), low HDL (OR=1.71 [1.14–2.55], p=0.01) and presence of metabolic syndrome (OR=2.20 [1.04–4.64], p=0.03) at baseline.*

### Conclusion

*We found a higher percentage of patients with severe vitamin D deficiency in early axial spondyloarthritis. Vitamin D deficiency was associated with higher disease activity and severity and presence of metabolic syndrome. Further longitudinal studies are required to evaluate the interest of vitamin D supplementation on the long-term outcome of the disease.*

**Key words**

vitamin D, disease activity, comorbidities, spondyloarthritis, DESIR cohort

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## Introduction

Apart from its important role to maintain homeostasis of calcium, phosphorus and bone metabolism, vitamin D seems also to have other roles in particular in the field of metabolic syndrome and immune system (1-2).

Recent studies have reported that vitamin D deficiency is associated with an increased risk of cardiovascular disease in the general population (3) in particular due to dyslipidaemia and metabolic syndrome (4). Potential mechanisms explaining the role of vitamin D include up-regulation of the renin-angiotensin-aldosterone system, adverse effects on vascular endothelial and smooth muscle function (5), and impaired glucose tolerance in vitamin D-deficient states (6).

Vitamin D seems to play a role for prevention of autoimmune disorders possibly through an immunomodulatory effect. Clinical studies have reported vitamin D as a potential immune modulator suppressing activated T cells and cell proliferation that may accelerate the inflammatory process (1, 7). In the field of spondyloarthritis, vitamin D status has been investigated mainly in patients with axial radiographic spondyloarthritis with contradictory results with regard to both the prevalence of vitamin D deficiency and the relationships between vitamin D status and disease activity/severity parameters (8-11). Moreover, all of these studies have been conducted in patients with an advanced disease making their interpretation difficult since vitamin D deficiency might result from immobilisation and functional disability, which prevent the patients from sunlight exposure.

The above arguments prompted us to take the opportunity to use the data collected in the French cohort of patients presenting inflammatory back pain suggestive of spondyloarthritis in order to investigate the vitamin D status in this population, compare it with the available data in the healthy French population, and evaluate the potential relationship existing between the vitamin D status and the activity/severity parameters of spondyloarthritis (12-14).

## Methods

*Study populations*

• *General healthy population*

The vitamin D status has been evaluated in a French population by the French Nutrition and Health Survey and previously reported (15).

• *DESIR cohort*

DESIR is a French prospective, multicentre, longitudinal cohort aiming to study patients with early inflammatory back pain suggestive of SpA (clinicaltrials.gov NCT01648907) (16).

This study fulfilled the current Good Clinical Practices and has obtained the approval of the local ethical committee "CPP Cochin hospital APHP Paris France.". Participants at the study gave their written informed consent. The website contains the detailed description of the centres, the organisation of the cohort and also the full detailed protocol and case-report form (17).

Briefly, consecutive patients aged >18 years and <50 years with IBP involving the thoracic, lumbar spine or buttock area for >3 months but <3 years and symptoms suggestive of SpA according to the rheumatologists' assessment (score ≥5 on a Numerical Rating Scale (NRS) of 0–10 where 0=not suggestive and 10=very suggestive of SpA) were included in the DESIR cohort. Patients had to fulfill the IBP criteria of Calin *et al*. (18) or Berlin (19).

Patients with a definite diagnosis of non-SpA back pain, conditions which might interfere with the validity of the informed consent and/or prevent an optimal compliance (*e.g*. alcoholism, psychiatric disorders) and a history of anti-tumour necrosis factor usage were excluded. Corticosteroid intake was permitted only in doses of <10 mg prednisone per day and had to be stable for at least 4 weeks before recruitment. For our study, patients were classified according to ASAS classification criteria for axial SpA (20).

*Data collected in the DESIR cohort*

• *Patient characteristics*

Age, gender, ethnicity and waist circumference were collected at baseline.

• *SpA characteristics*

All the items permitting to adequately

classify a patient according to the ASAS criteria were collected at baseline.

The activity of the disease was evaluated using the following parameters: BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) (21), and ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score – C-reactive protein) (22). The severity of the disease was assessed using the following parameters: BASFI (Bath Ankylosing Spondylitis Functional Index) (23) and BASMI (Back Ankylosing Spondylitis Metrology Index) (24). These measures were collected at baseline and thereafter every 6 months until the two year follow-up visit.

• *Radiographic, MRI and BMD measurements*

The imaging modalities were previously described (25). Conventional pelvic x-rays were performed at baseline in all patients. Radiologists or rheumatologists at each study centre scored each sacroiliac joint (SIJ) as follows: 0=normal, 1=doubtful, 2=obviously abnormal or 3=fused. SIJs were considered abnormal if at least one SIJ was scored 2 or 3. MRI scans of the SIJs, upper spine (C2 to T10) and lower spine (T8 to S1) were performed using the short-tau inversion recovery (STIR) and T1 fast spin echo (FSE) acquisitions. Radiologists or rheumatologists at each study centre assessed the presence of inflammatory and structural damage at the SIJs and spine. For each of these MRI evaluations, radiologists or rheumatologists at each study centre scored as follows: 0=normal, 1=doubtful, 2=abnormal. MRI was considered abnormal only if scored as "abnormal" by the rheumatologist or radiologist.

BMD was measured by dual-energy x-ray absorptiometry at baseline in a sub-group of patients using Hologic, Inc. or Lunar (GE Healthcare) devices by experienced investigators. BMD was determined at the lumbar spine (second to fourth vertebrae) and the upper part of the left femur (total femur and femoral neck). The results were given as BMD (g/cm$^2$). We used the threshold of −2 SD in Z score for the definition of low BMD according to the International Society of Clinical Densitometry; the WHO definition based on T scores cannot be applied in non-menopausal women and men below 50 years (26).

• *Metabolic syndrome*

Metabolic syndrome (MetS) was defined by the presence of any three of the following five characteristics according to the National Cholesterol Education Programme's Adult Treatment Panel III report: 1) increased waist circumference (>102 cm [>40 in] for men, >88 cm >35 in] for women); 2) elevated triglycerides (≥150 mg/dl); 3) low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women); 4) hypertension (≥130/≥85 mmHg); and 5) impaired fasting glucose (≥110 mg/dl) (27).

• *Biochemical measurements*

Plasma fasting glucose (FG) levels, triglycerides and high-density lipoprotein (HDL) were determined at baseline by standard laboratory methods. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) were evaluated every 6 months during the two-year follow-up period.

*Vitamin D evaluation*

The values observed in the French general population according to age were taken from the French Nutrition and Health Study (ENNS) carried out in 2006-2007 (15). The technique used for the control was the IDS gamma-B-2J hydroxy vitamin D (Immunodiagnostic Systems France SA, Paris). Given the available data in the French population, we have taken the group of patients aged 30–54 years old to compare with the DESIR patients.

One biological resources centre (Paris Bichat, Joëlle Benessiano) was in charge of centralising and managing biological data collection in the DESIR cohort. The technique used for the patients in the DESIR cohort was the chemiluminiscent immunoassay IDS-ISYS (immunodiagnostic system, Boldon, England).The inter-assay coefficient variations of this technique ranges from 8.9% to 16.9%.

Vitamin D deficiency was defined as <50 nmol/Land severe deficiency less than 25 nmol/L (28).

*Statistical analysis*

The statistical analysis was performed in several steps on the DESIR database locked on October 30, 2012.

We first evaluated the distribution of the vitamin D status in the patients of the DESIR cohort at baseline and checked the influence of well-known factors such as ethnicity and time of collection (*e.g.* the different 4 seasons of a year). Thereafter, we compared the percentage of patients with a vitamin D deficiency in this cohort and in the healthy French population matched for age.

Secondly, we evaluated the vitamin D status in different groups of patients of the DESIR cohort according to their phenotype based on the different arms of the ASAS criteria. For this purpose, we classified each patient according to the ASAS criteria for axial spondyloarthritis resulting in the following three categories:

1. patients not fulfilling the ASAS criteria,
2. patients fulfilling the ASAS criteria when imaging findings permitted to classify them in the "imaging" arm,
3. patients fulfilling the ASAS criteria when imaging findings permitted to classify them in "clinical arm".

Since all the patients of the cohort were included based on the presence of inflammatory back pain (*e.g.* one spondyloarthritis feature), the patients were "classified" in the imaging arm in case of demonstration of an objective sign of inflammation at MRI or of structural damage (conventional pelvic x-ray) in the SIJs. In case such imaging modalities were normal or doubtful, the patients were "classified" in the clinical arm in case of HLA B27 positivity and at least another (*e.g.* apart from inflammatory back pain) spondyloarthritis feature (*e.g.* dactylitis, enthesitis, psoriasis, uveitis, etc.).

Moreover, because different scenarios can be observed according to both the imaging modalities and the CRP status considering a value ≥6 mg as reflecting an elevated CRP, we performed a descriptive analysis in eight different subgroups: *a*) x-ray definite SIJ damage and MRI inflammatory changes of the SIJ and CRP abnormal, *b*) x-ray definite SIJ damage and MRI inflammatory changes of the SIJ and CRP normal, *c*)

x-ray definite SIJ damage and MRI SIJ normal and CRP abnormal, *d*) x-ray definite SIJ damage and MRI SIJ normal and CRP normal, *e*) x-ray SIJ normal and MRI inflammatory changes of the SIJ and CRP abnormal, *f*) x-ray SIJ normal and MRI inflammatory changes of the SIJ and CRP normal. For the clinical arm, we defined two groups: a) x-ray SIJ normal and MRI SIJ normal and CRP abnormal, and b) x-ray SIJ normal and MRI SIJ normal and CRP normal.

Thirdly, in order, to evaluate the potential correlations existing between Vitamin D status and disease characteristics at baseline, we compared the demographic and disease characteristics with regard to the vitamin D status (deficiency/not deficiency), by *t*-student test and Fisher's tests as appropriate. Logistic regression was used to model the association of socio-demographic, and disease characteristics with vitamin D level adjusted on ethnicity and time (season) of data collection. Thereafter, we evaluated such potential correlations between vitamin D baseline status and the mean values of the different parameters evaluating the activity and the severity of the disease collected during the first two year follow-up. For this latter analysis, we performed a multiple logistic regression adjusted not only on ethnicity and time of collection but also on anti-TNF therapy.

Finally, we studied the presence of comorbidities according to the vitamin D level by comparing the percentage of patients presenting comorbidities in patients with or without vitamin D deficiency at baseline. Multivariate logistic regression was performed adjusted on ethnicity and season. Osteoporosis was defined as a T-score under -2 SD, either at the lumbar region or the femoral neck (26). Metabolic syndrome (MetS) was defined according to the National Cholesterol Education Programme's Adult Treatment Panel III report (27).

Statistical analysis was performed with the SAS v. 9.3. *p*-values<0.05 were regarded as significant.

## Results

*Vitamin D status in the two study populations*

A total of 700 patients were analysed in the DESIR cohort including 486 (69.4%) who met ASAS criteria. The mean vitamin D was 54.2±28.7 nmol/L. Any deficiency and severe deficiency were observed in 51% *versus* 41% and in 11.7% *versus* 5% in the DESIR cohort *versus* the healthy French population respectively. In the DESIR cohort, this deficiency was more pronounced in winter-spring than summer-autumn (57% *vs*. 42% respectively, $p<0.001$) and in non-Caucasian patients than caucasians (24% *vs*. 7%, $p=0.003$). There was no statistically significant association with other patients' characteristics such as age, gender and vitamin D levels.

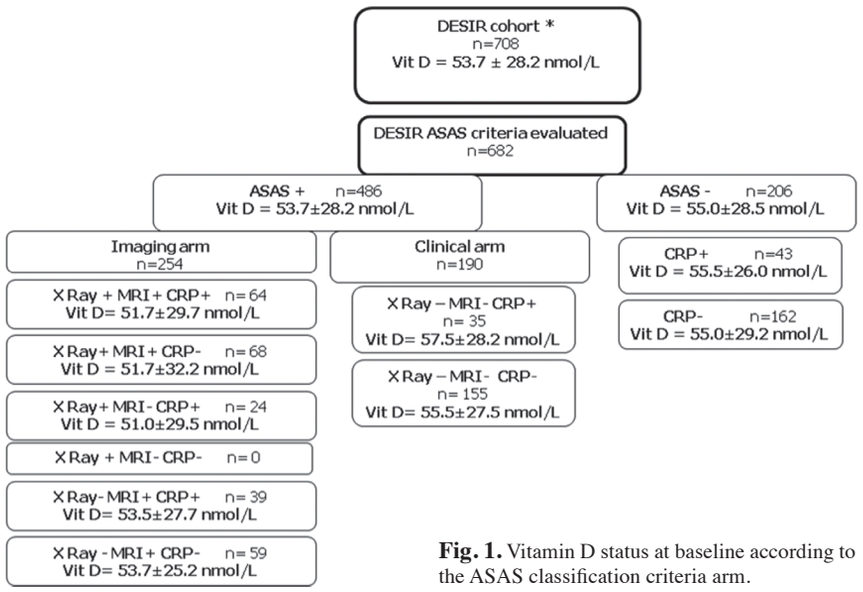


**Fig. 1.** Vitamin D status at baseline according to the ASAS classification criteria arm.

*Vitamin D status with regard to the ASAS classification criteria arms at baseline*

Figure 1 shows the vitamin D levels at baseline in different sub-groups of patients with regard to the ASAS classification criteria arms.

Apart from a trend in lower vitamin D levels in patients in the different "radiographic" arms, there was no statistically significant difference in the vitamin D levels in the different evaluated sub-groups of patients.

*Relationship between vitamin D deficiency and SpA disease activity and severity at baseline*

The demographic and disease characteristics of the SpA patients according to vitamin D status are showed in Table I. After adjusting for season and ethnicity, vitamin D deficiency remained significantly associated with baseline radiological sacroiliitis (OR=1.51 [1.03–2.23], $p=0.03$), higher baseline ASAS score (OR=1.63 [1.07–2.48], $p=0.02$), and higher baseline BASDAI (OR=1.46 [1.04–2.07], $p=0.03$). At variance, we failed to demonstrate a statistically significant correlation between vitamin D deficiency and the clinical parameters evaluating the severity of the disease such as the BASFI and BASMI indices.

*Relationship between vitamin D deficiency at baseline and SpA disease activity and severity during the first 2 years of disease follow-up*

After 2 years of follow-up, patients with baseline vitamin D deficiency had higher mean (m) BASDAI (39.8±18.9 *vs*. 37.5±17.7; $p=0.11$), mBASFI (28.0±20.8 *vs*. 24.5±18.8; $p=0.02$), mBASMI (2.4±0.9 *vs*. 2.3±0.8; $p=0.05$) and mASDAS score (2.3±0.9 *vs*. 2.1±0.8, $p=0.02$). After adjusting on season, ethnicity and biotherapy, there was a trend (but not statistically significant) in favor of a relationship between baseline vitamin D deficiency and higher mean ASDAS and higher mean BASFI (Table II).

*Association between vitamin D deficiency and comorbidities*

In multivariate analysis, vitamin D deficiency was significantly associated with the presence of abdominal obesity

**Table I.** Relationship between vitamin D deficiency and SpA disease activity and severity at baseline.

| | DESIR cohort n=708 n (%) | Patients with VitD <50 nmol/L n=358 n (%) | Patients with VitD >50 nmol/L n=342 n (%) | *p*-value[1] | *p*-value adjusted[2] |
|---|---|---|---|---|---|
| Gender female, n(%) | 381 (53.8) | 193 (53.9) | 184 (46.2) | 0.97 | |
| Age (years), mean±SD | 33.7 ± 8.6 | 3.8 ± 8.8 | 33.7 ± 8.4 | 0.81 | |
| Winter*, n(%) | 408 (57.8) | 282 (79.0) | 126 (36.8) | <0.001 | |
| No Caucasian, n(%) | 635 (89.8) | 49 (13.4) | 23 (6.7) | <0.001 | |
| ASAS+, n(%) | 486 (70.2) | 252 (71.6) | 229 (68.8) | 0.42 | |
| X-Ray +, n(%) | 187 (27.0) | 104 (29.6) | 81 (24.1) | 0.10 | |
| MRI+ n(%) | 231 (33.6) | 123 (35.2) | 105 (31.7) | 0.33 | |
| BASDAI ≥40, n(%) | 425 (60.4) | 226 (63.5) | 193 (56.8) | 0.07 | 0.03 |
| BASFI, mean ± SD | 30.4 ± 22.8 | 31.6 ± 23.2 | 29.0 ± 22.2 | 0.18 | 0.19 |
| BASMI, mean ± SD | 2.4 ± 1.0 | 2.5 ± 1.0 | 2.3 ± 0.9 | 0.01 | 0.14 |
| ASDAS crp, mean ± SD | 2.5 ± 1.0 | 2.5 ± 1.0 | 2.4 ± 1.1 | 0.10 | 0.18 |
| ASDAScrp ≥ med, n (%) | 339 (50.2) | 182 (54.5) | 151 (45.1) | 0.01 | 0.02 |
| ASDAS crp<1.3, n (%) | 86 (12.72) | 35 (10.48) | 51 (15.2) | 0.03 | 0.05 |
| CRP, mean ± SD | 8.1 ± 13.5 | 8.0 ± 12.5 | 8.2 ± 14.5 | 0.23 | 0.94 |

DESIR cohort: cohort of patients suffering from inflammatory back pain suggestive of spondyloarthritis; ASAS+: Patients fulfilling the ASAS classification criteria for the diagnosis of axial spondyloarthritis; x-ray+ : Presence of obvious (investigators opinion) structural damage of the sacroiliac joints on pelvic plane x-ray; MRI+ : Presence of obvious (investigator's opinion), inflammatory lesion of the sacroiliac joints on pelvic MRI; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Back Ankylosing Spondylitis Metrology Index; ASDAScrp : Ankylosing Spondylitis Disease Activity Score-C-reactive protein; CRP: C-reactive protein. *Annual season of vitamin D evaluation; [1] *p*-value associated to the level of vitamin D; [2] *p*-value associated to the level of vitamin D adjusted on ethnic and season.

**Table II.** Relationship between vitamin D deficiency at baseline and SpA disease activity and severity during the first two years of disease follow-up

| | Whole study patients n=708 | Patients with VitD ≤50 nmol/L n=358 | Patients with VitD >50 nmol/L n=342 | *p*-value[1] | *p*-value adjusted[2] |
|---|---|---|---|---|---|
| mBASDAI, mean±SD | 38.8 ± 18.3 | 40.2 ± 18.5 | 37.1 ± 17.7 | 0.03 | 0.12 |
| mBASFI, mean±SD | 26.0 ± 19.8 | 27.8 ± 20.4 | 24.2 ± 19.0 | 0.02 | 0.07 |
| mBASMI, mean±SD | 2.3 ± 0.8 | 2.4 ± 0.9 | 2.3 ± 0.8 | 0.02 | 0.23 |
| mASDAS, mean±SD | 2.2 ± 0.8 | 2.3 ± 0.8 | 2.1 ± 0.8 | 0.02 | 0.07 |
| mCRP, mean±SD | 6.1 ± 7.3 | 6.5 ± 7.7 | 5.6 ± 7.0 | 0.14 | 0.22 |

mBASDAI: mean BASDAI, mBASFI: mean BASFI, mBASMI: mean BASMI, mASDAS: mean ASDAS over two years. [1] statistical significance based on the inter-group comparison; [2] the adjustment has been made on ethnicity, annual season of vitamin D evaluation and anti-TNF therapy.

(OR =1.65 [1.05–2.61], *p*=0.03), low HDL (OR=1.71 [1.14–2.55], *p*=0.01) and presence of the metabolic syndrome (OR = 2.20 [1.04–4.64], *p*=0.04) at baseline (Table III).

The associations between vitamin D deficiency (<20 ng/mL) and abdominal adiposity, low HDL, and presence of metabolic syndrome are presented in Table IV. In all of the 3 analyses evaluating the factors associated with co-morbidities (*e.g.* metabolic syndrome, abdominal obesity, low HDL level of cholesterol), functional disability evaluated by the BASFI was picked-up. Moreover, vitamin D deficiency was also recognised as an associated factor of abdominal obesity and low HDL cholesterol levels.

## Discussion

We evaluated the vitamin D status in patients presenting inflammatory back pain suggestive of spondyloarthritis, compared it with the available data in the healthy French population, and investigated the potential relationship existing between the vitamin D status and the activity/severity parameters of spondyloarthritis. The main finding was a higher prevalence of vitamin D deficiency in spondyloarthritis at the onset of the disease and also that such deficiency might be correlated with a more active and severe disease.

Our findings related to the times of evaluation (*e.g.* season) are perfectly in line with the published data in this area. In fact, vitamin D metabolism may be influenced by sunlight exposure and season (lower levels between October and April) (29). Ethnicity has been also previously reported to be an important factor influencing the vitamin D metabolism. In our study, the majority of the non-Caucasian were of an Arabic origin. In Arabs, the prevalence of vitamin D deficiency has been reported as high as 77% (30). Studies in this population suggest that the dress habits are not the single explanation of these findings, which might be related also to genetic factors (31-32).

We found in our study that vitamin D deficiency was significantly associated with baseline radiological sacroiliitis. Few authors described this association only in case of ostemalacia (33-35). The physiopathological way is not yet elucidated. One hypothesis might be that "sacroiliitis" could be attributable to subchondral bone changes related to the metabolic bone diseases.

This study also confirms well known data concerning the vitamin D levels and markers of atherosclerosis such as abdominal obesity and cholesterol levels. Indeed, vitamin D has been associated with atherosclerosis at each stage of its development from subclinical plaque to the associated cardiovascular morbidity and mortality (36). Also, the relationship between vitamin D deficiency and dyslipidemia may be due, in part, to vitamin D effects on hepatic lipid metabolism (37). Alternatively, vitamin D sequestered in body fat, and obesity may be associated with a decreased bioavailability of the hormone (38).

Although the French population is known to have endemic vitamin D deficiency (15), our study suggests a higher prevalence of such deficiency in patients presenting with inflammatory back pain suggestive of spondyloarthritis. However, the comparison between the DESIR cohort patients and the historical cohort of the healthy French population might be hazardous since the techniques used

**Table III.** Presence of comorbidities according to the Vitamin D level.

| | Whole study patients n=708 | Patients with VitD ≤50 nmol/L n=358 | Patients with VitD ≤50 nmol/L n=342 | *p*-value[1] | *p*-value adjusted[2] |
|---|---|---|---|---|---|
| Abdominal obesity [a], % | 122 (17.9) | 71 (20.8%) | 49 (14.9%) | 0.04 | 0.03 |
| Triglycerides>150mg/dl, % | 94 (14.3%) | 48 (14.3%) | 46 (14.5%) | 0.94 | 0.61 |
| Low HDL CT[b], % | 176 (28.2%) | 103 (32.8%) | 72 (23.7%) | 0.01 | 0.01 |
| Blood pressure>130/85mmHG,% | 98 (14.2%) | 50 (14.4%) | 46 (13.8%) | 0.84 | 0.87 |
| Fasting glucose>6.05 mmol/l, % | 21 (3.1%) | 13 (3.8%) | 7 (2.1%) | 0.20 | 0.11 |
| Metabolic syndrome[c], % | 40 (5.7%) | 26 (7.3%) | 14 (4.1%) | 0.07 | 0.04 |
| Cardiovascular event[d], % | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | - | - |
| Fatigue, mean ± SD | 5.7 ± 2.3 | 5.8 ± 2.3 | 5.5 ± 2.4 | 0.30 | 0.17 |
| Spine Tscore, mean ± SD | -0.35 ± 1.31 | -0.42 ± 1.31 | -0.29 ± 1.33 | 0.40 | 0.16 |
| Hip Neck Tscore, mean ± SD | -0.35 ± 1.18 | -0.42 ± 1.10 | -0.27 ± 1.26 | 0.28 | 0.09 |
| Hip Tscore, mean ± SD | -0.16 ± 1.10 | -0.21 ± 1.09 | -0.10 ± 1.13 | 0.44 | 0.23 |
| Osteoporosis*, % | 54 (16.5%) | 27 (16.1%) | 27 (17.0%) | 0.82 | 0.83 |

[a] Abdominal obesity: Waist circumference >102 cm for men and > 88 cm for women; [b] HDL Cholesterol <1.04 mmol/l for men and <1.29 mmol/l for women; [c] Metabolic syndrome was defined by the presence of any three of the following five characteristics according to the National Cholesterol Education Program's Adult Treatment Panel III report: 1) increased waist circumference (>102 cm [>40 in] for men, >88 cm [>35 in] for women); 2) elevated triglycerides (≥150 mg/dl); 3) low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women); 4) hypertension (≥130/≥85 mmHg); and 5) impaired fasting glucose (≥110 mg/dl) [24].*osteoporosis was defined by a T score ≤2 standard deviation observed at either the lombar (L1-L4) spine, total hip or femoral neck location (23); [d] at least one cardiovascular event at baseline: myocardial ischaemia, stroke; [1] *p*-value associated to the level of vitamin D;
[2] *p*-value associated to the level of vitamin D adjusted on ethnic and season.

to evaluate the vitamin D level were different.

Contradictory results have been previously reported in patients suffering from advanced definite axial radiographic spondyloarthritis with studies showing a low vitamin D level in patients in comparison to healthy persons (9, 39) while other studies have found no difference between patients and controls (8). One explanation concerning the vitamin D deficiency in advance axial disease is that immobilisation and functional disability (which prevent the patients from sunlight exposure) might be responsible for the decrease in vitamin D level. However, our study conducted in patients at the onset of that disease is also in favour of a higher prevalence of vitamin D deficiency suggesting that a decrease in vitamin D level might result in an increase in the inflammatory process (9).

Our study suggests also that such vitamin D deficiency is more frequently observed in patients with a high active disease. Such findings were in line with literature. We showed in a previous cross-sectional study that in comparison with the control group, male axial spondyloarthritis patients showed significantly decreased vitamin D. The level of vitamin D was negatively correlated to BASDAI without any changes after adjustment for age, duration of disease, sunlight exposure, and total taking steroids (40). Also, Lange *et al*. observed that high disease activity in axial spondyloarthritis is associated with an alteration in vitamin D metabolism, increased bone resorption (8). Obermayer *et al*. suggested a close association of BMD, bone metabolism, and inflammatory activity with Fok1 polymorphisms of the vitamin D receptor gene in male axial spondyloarthritis patients (41).

This study has some limitation but also many strengths. The control population has not been evaluated in the same condition as the patients and we do recognise the potential pitfalls concerning the strict comparison between the DESIR patients and the historical control of the healthy French population. However, we tried to minimise this criticism by matching the controls on age. Moreover, the large number of evaluated patients (*e.g*. 700) probably allows a relevant interpretation of the observed results. Another limitation of our study may be that the vitamin D level at baseline does not reflect the status at the onset of the disease, but just a picture at one moment in time.

In our study, the fact that we have not assessed the dietary vitamin D intake, the frequency and amount of sunlight exposure, the geographical distribution of cases, the body fat and serum levels of fat soluble vitamins and the mobility/sedentarity can be also seen as a weakness of the study methodology. However, we would like to emphasise the fact that this was not the objective of this study. Also this potential confounding factor probably does not have a great impact on our findings especially regarding the correlation between vitamin D deficiency and the disease activity parameters because this study was conducted at the onset stage of the disease. Most of our patients were not disabled. However, low 25 OH vitamin D might be a consequence and not the cause of spondyloarthritis and at the same time, low 25 OH vitamin D might result in a more severe and active disease that creates a negative feedback loop.

Finally, the strengths of this study are probably related to both the quality of the collected data and the longitudinal design of the study. DESIR is a prospective longitudinal follow up of patients presenting with inflammatory back pain. The patients are closely monitored (every 6 months) in 20 different centres using a standardised Case Report Form. Such study is conducted in accordance with the Good Clinical Practices and in particular monitored by a Clinical Research Unit in charge of the detection and correction of missing and/or aberrant information (17).

The longitudinal aspect of the design of our study can be seen as a strength. Its design permitted the evaluation of the correlations existing between vitamin D levels and disease activity/severity parameters not only at baseline (cross-sectional study) but also between such baseline vitamin D levels and the disease activity/severity parameters of the disease during the first two years of the disease.

Our findings suggest that a systematic evaluation of vitamin D status seems logical in patients presenting with inflammatory back pain suggestive of

**Table IV.** Univariate and multivariate analysis of presence of comorbidities with regard to baseline vitamin D and patient/disease characteristics.

| ABDOMINAL OBESITY | | | | |
|---|---|---|---|---|
| | Patients with abdominal obesity n=122 | Patients without abdominal obesity n=558 | *p*-value | Multivariate analysis OR [IC 95%] |
| Vitamin D, mean ± SD | 48.0 ± 25.5 | 55.7 ± 29.5 | | |
| Low Vitamin D, n(%) | 71 (59.2%) | 271 (49.1%) | 0.04 | 1.64 [1.07 – 2.53] |
| ASDAScrp≥median, n(%) | 68 (57.1%) | 255 (47.8%) | 0.06 | - |
| BASFI ≥ median, n(%) | 78 (65.6%) | 258 (46.6%) | <0.0001 | 2.19 [1.41 – 3.41] |
| BASMI ≥ median, n(%) | 67 (56.3%) | 297 (54.7%) | 0.75 | - |
| Caucasian, n(%) | 109 (89.3%) | 501 (89.8%) | 0.88 | - |
| Winter, n(%) | 71 (58.2%) | 322 (57.9%) | 0.95 | - |
| Sex (female), n(%) | 26 (21.3%) | 271 (51.3%) | <0.0001 | 0.26 [0.16 – 0.43] |
| Psoriasis, n(%) | 30 (24.6%) | 77 (13.8%) | 0.003 | 1.94 [1.14 – 3.29] |
| LOW HDL | | | | |
| | Patients with low HDL n=176 | Patients without low HDL n=448 | *p*-value | Multivariate analysis OR [IC 95%] |
| Vitamin D, mean ± SD | 50.2 ± 25.0 | 56.25 ± 29.5 | 0.03 | |
| Low Vitamin D, n(%) | 103 (58.9%) | 211 (47.6%) | 0.01 | 1.49 [1.03 – 2.17] |
| ASDAScrp≥median, n(%) | 90 (52.9%) | 200 (46.2%) | 0.13 | - |
| BASFI≥median, n(%) | 100 (57.1%) | 204 (46.0%) | 0.01 | 1.60 [1.11 – 2.32] |
| BASMI≥median, n(%) | 102 (61.1%) | 231 (52.5%) | 0.05 | - |
| Caucasian, n (%) | 157 (89.2%) | 408 (91.1%) | 0.47 | - |
| Winter, n (%) | 100 (57.1%) | 254 (56.7%) | 0.92 | - |
| Sex (female), n (%) | 90 (51.1%) | 245 (54.7%) | 0.42 | - |
| Psoriasis, n (%) | 147 (83.5%) | 371 (82.8%) | 0.92 | 1.02 [0.64 – 1.64] |
| METABOLIC SYNDROME | | | | |
| | Patients with metabolic syndrome n=40 | Patients without metabolic syndrome n=668 | *p*-value[1] | Multivariate analysis OR [IC 95%] |
| Vitamin D, mean ± SD | 47.5 ± 27.2 | 54.7 ± 28.7 | | |
| Low Vitamin D, n (%) | 26 (65.0%) | 332 (50.3%) | 0.07 | - |
| ASDAScrp ≥median, n (%) | 26 (65.0%) | 313 (49.2%) | 0.05 | - |
| BASFI ≥median, n (%) | 29 (72.5%) | 323 (48.9%) | <0.001 | 2.85 [1.40 – 5.80] |
| BASMI ≥median, n (%) | 23 (57.5%) | 359 (55.7%) | 0.82 | - |
| Caucasian, n (%) | 38 (95.0%) | 597 (89.5%) | 0.41 | - |
| Winter, n (%) | 24 (60.0%) | 384 (57.7%) | 0.77 | - |
| Sex (female), n (%) | 20 (50.0%) | 307 (46.0%) | 0.62 | - |
| Psoriasis, n (%) | 13 (32.5%) | 97 (14.6%) | 0.003 | 2.50 [1.12 – 5.06] |

ASDAScrp: Ankylosing Spondylitis Disease Activity Score – C-reactive protein; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Back Ankylosing Spondylitis Metrology Index. [1]*p*-value associated to comorbidities adjusted on ethnic, season, sex, Vitamin D<20 ng/ml, ASDAScrp ≥median, BASFI ≥median, BASMI ≥median.

spondyloarthritis. However, other studies have to be conducted in order to confirm or not confirm such data and in particular the correlations and the physiopathological pathway existing between/explaining the vitamin D deficiency and the activity of the disease. Finally, further longitudinal studies are required to evaluate the interest of vitamin D supplementation on the long-term outcome of the disease.

**Key messages**

- Vitamin D deficiency was associated with higher disease activity and severity in early axial spondyloarthritis.
- Vitamin D deficiency was associated with metabolic syndrome in early axial spondyloarthritis.
- We suggest a systematic evaluation of vitamin D status in suggesting spondyloarthritis.

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