Systematic review of association between vitamin D levels and susceptibility and disease activity of ankylosing spondylitis

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Abstract

Objectives. Vitamin D appears to have significant effects on both innate and acquired immunity and deficiency may be associated with both susceptibility and disease severity in some autoimmune conditions. There has been little focus on the potential immunomodulatory role of vitamin D in AS. This study systematically reviews the evidence for an association between vitamin D deficiency and disease susceptibility and severity in AS.


Results. Fifteen original articles and five conference abstracts met the criteria for inclusion. All were cross-sectional in design. Seven of 11 studies identified lower concentrations of 25-hydroxyvitamin D (25OHD) in AS patients compared with healthy controls. A significant inverse correlation between 25OHD and disease activity was observed in 5 of 11 studies. The majority of studies that failed to demonstrate significant findings used inappropriate statistical methods.

Conclusion. Cross-sectional studies using appropriate statistical analyses have highlighted that AS is associated with lower vitamin D concentrations. Within groups of AS patients there is some evidence that low vitamin D concentrations are associated with higher disease activity. However, there are insufficient published data to support an immunomodulatory role for vitamin D in AS. Further study with a longitudinal design is required to understand whether optimizing vitamin D in AS has potential as a disease-modifying intervention.

Key words: vitamin D, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, ankylosing spondylitis, axial spondyloarthritis, disease activity, anti-TNF, cross-sectional.

Introduction

Geographical epidemiological studies have demonstrated a higher disease prevalence of some autoimmune and rheumatic diseases in populations with increasing latitudes [1]. This is most evident for multiple sclerosis [1], but is also described in RA [2] and AS [3]. This increased prevalence of autoimmune disease may be due to geographical variability in diet, infection or possibly due to genetic risk factors concentrated in these populations. However, an alternative explanation may be that vitamin D deficiency, caused by reduced ultraviolet B (UVB) exposure, contributes to the development and progression of autoimmune disease. In support of this hypothesis, seasonal variance has been observed in RA, with season of onset influencing joint damage progression [6] and disease activity levels varying with season [2, 4]. In addition, interventional studies with the vitamin D analogue alphacalcidol reduced disease activity in RA [5] and reduced proinflammatory cells and cytokines in mixed CTD [6].

There is evidence that vitamin D influences both the innate and adaptive immune systems [7]. Cells of the innate immune system (monocytes/macrophages and
dendritic cells) express 1-alpha-hydroxylase (CP27B) and vitamin D receptor (VDR) and can utilize vitamin D for autocrine responses via localized conversion to the active metabolite 1,25-dihydroxyvitamin D (1,25-D). In the adaptive immune system, 1,25-D reduces proinflammatory T helper 1 (Th1) and Th17 cell activity and supports Th2 and regulatory T cells that increase immune tolerance [7]. 1,25-D also reduces B cell proliferation and differentiation. These actions of vitamin D make it a potentially important modulator of autoimmunity.

In AS, the pathological process is that of inflammation and ossification with evidence for accelerated bone loss [8]. Therefore vitamin D may play a role in the development and progression of disease. Treatment in AS is mainly symptomatic and few drugs actually slow the disease process [9]. Therefore, exploring whether vitamin D influences the disease process is important, as this could highlight new or adjunct treatment options. The aim of this review was to systematically identify and analyse all studies that contribute data on vitamin D and AS to determine whether vitamin D has immunomodulatory or pathophysiological roles in this condition.

Methods

Search strategy and selection criteria

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using a predetermined protocol. Medline (including Medline in-progress and Medline daily update), EMBASE, Web of Science and the Cochrane Library were searched independently by two reviewers in December 2013 using the following terms: vitamin D AND ankylosing spondylitis OR axial spondyloarthritis. Preliminary searches with differential nomenclature for vitamin D (calcifediol, calcitriol, etc.) did not affect results. Results were limited to human studies. Abstract lists from the European League Against Rheumatism (2002–13), British Society for Rheumatology (1993–2013) and ACR (2006–13) were also searched.

Studies were included if they reported original results with relevance to vitamin D metabolites and AS or axial spondyloarthritis (axSpA). Studies were excluded where data on AS could not be isolated from grouped data or where the discussion did not provide raw data (in the case of abstracts). The search returned many studies that made reference to vitamin D as a supplement in AS studies; these were also excluded.

Data extraction and bias

Two authors independently confirmed the eligibility of studies and extracted data from the qualifying studies. Any discrepancies were resolved through discussion. Selected studies were summarized into a data extraction form. Information included sample size, medications, control for seasonal variation, vitamin D metabolite levels and their correlation with markers of disease activity. For comparison, studies were assessed for bias using an adapted Newcastle–Ottawa Scale (NOS) as suggested for Cochrane reviews of non-randomized studies [10]. This is a star system, where studies are judged on three broad perspectives: four stars available for selection of cases and controls, two for comparability of the groups (chosen in this review to be control for seasonal variation and details on the use of vitamin D-containing therapy) and three for the ascertainment of exposure (one star for a description of the assay technique for assessment of exposure).

Results

The search strategy identified 82 unique publications, the titles and abstracts of which were screened for inclusion. The full text of 16 articles and 10 abstracts was retrieved, of which 15 articles and 5 abstracts met the inclusion criteria (see flowchart, Supplementary Fig. S1, available at Rheumatology Online). The reason for exclusion was the lack of raw data. Attempts were made to contact corresponding authors of all excluded studies as well as included studies where information was lacking.

There were no studies with longitudinal data. Nine articles [8, 11–18] and two abstracts [19, 20] studied AS patients with healthy controls matched for age and gender. One study used PsA patients as controls and was excluded, as it could not be meaningfully compared [21].

Three articles [22–24] and two abstracts [25, 26] reported cross-sectional studies within AS cohorts with no controls. One abstract studied a large cross-sectional cohort of axSpA patients [27]. Results from the literature search also identified studies of VDR polymorphisms [16], vitamin D binding protein (DBP) [28] and one mass spectrometry study for biomarkers in AS [29]. These will be discussed separately.

The modified New York criteria for AS [30] was consistently used for patient selection in all studies. Only one abstract used the more recent Assessment of SpondyloArthritis international Society (ASAS) criteria for axSpA to define cases [27].

The studies varied widely in sample size, from 14 to 128 AS patients, and one abstract had 653 axSpA patients. There was also considerable heterogeneity between studies in adjustment for season of testing of vitamin D levels.

Only 6 of the 20 studies specified the primary aim of assessing the effect of vitamin D on disease activity [12, 20, 26, 27, 31, 32]. All other studies evaluated vitamin D as part of multiple outcomes in the context of bone metabolism. Only one study specified calculation for power and sample size [31]. In eight studies, tests for normality of data were performed and/or non-parametric tests were used for comparison. Five studies stated the use of parametric tests despite vitamin D being a variable that is not normally distributed [12, 13, 26, 32, L. Muntean, personal communication].

Comparing vitamin D between AS and healthy controls

Eleven studies assessed 25OHD levels in AS and healthy controls, four of these also assessed 1,25-D. The results are summarized in Table 1. Vitamin D is not a normally
### Table 1: Comparative summary of studies assessing 25OHD and 1,25-D in AS patients and healthy controls

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Medication</th>
<th>Vitamin D metabolite</th>
<th>Control for seasonal variation</th>
<th>Patient serum level</th>
<th>Control serum level</th>
<th>Statistically significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mermerci Baskan et al. [15]</td>
<td>100 58</td>
<td>Not excluded</td>
<td>25OHD, nmol/l</td>
<td>21.7 (12.2)</td>
<td>No</td>
<td>32.7 (8.8)</td>
<td>Yes (P &lt; 0.0001)</td>
</tr>
<tr>
<td>Lange et al. [8]</td>
<td>58 58</td>
<td>Not excluded</td>
<td>25OHD, nmol/l</td>
<td>47.6 (24.4)</td>
<td>Summer</td>
<td>72.5 (17.5)</td>
<td>Yes (P &lt; 0.05)</td>
</tr>
<tr>
<td>Lange et al. [14]</td>
<td>70 45</td>
<td>Not excluded</td>
<td>1,25D, pmol/l</td>
<td>65.3 (20.7)</td>
<td>May-August</td>
<td>103.2 (24)</td>
<td>Yes (P &lt; 0.05)</td>
</tr>
<tr>
<td>Hmamouchi et al. [18]</td>
<td>70 140</td>
<td>Not excluded</td>
<td>25OHD, nmol/l</td>
<td>55 (2.5)</td>
<td>Summer</td>
<td>60 (27.5)</td>
<td>Yes (P &lt; 0.05)</td>
</tr>
<tr>
<td>Erten et al. [31]</td>
<td>48 92</td>
<td>Not excluded</td>
<td>1,25D, pmol/l</td>
<td>74.4 (31.2)</td>
<td>May-August</td>
<td>100.8 (31.2)</td>
<td>Yes (P &lt; 0.05)</td>
</tr>
<tr>
<td>Obermayer-Pietsch et al. [16]</td>
<td>104 54</td>
<td>Not excluded</td>
<td>25OHD, nmol/l</td>
<td>51.7 (26.5)</td>
<td>No comment</td>
<td>60.8 (4%)</td>
<td>Yes (P = 0.004)</td>
</tr>
<tr>
<td>Franck and Keck [13]</td>
<td>38 52</td>
<td>Not excluded</td>
<td>25OHD, nmol/l</td>
<td>54 (33.8)</td>
<td>No comment</td>
<td>50.3 (8)</td>
<td>No (a)</td>
</tr>
<tr>
<td>Durmus et al. [12]</td>
<td>99 42</td>
<td>Excluded</td>
<td>25OHD, nmol/l</td>
<td>153.6 (82.8)</td>
<td>June-August</td>
<td>125.8 (16.1)</td>
<td>No (a)</td>
</tr>
<tr>
<td>Yazmalar et al. [32]</td>
<td>72 70</td>
<td>Not excluded</td>
<td>25OHD, nmol/l</td>
<td>67 (29.3)</td>
<td>Summer</td>
<td>77.8 (38.8)</td>
<td>No (a)</td>
</tr>
<tr>
<td>Abstract Baykal et al. [19]</td>
<td>40 35</td>
<td>Not excluded</td>
<td>25OHD, nmol/l</td>
<td>77.0 (57.2)</td>
<td>Winter</td>
<td>76.8 (46.3)</td>
<td>No (a)</td>
</tr>
<tr>
<td>Abstract Muntean et al. [20]</td>
<td>44 39</td>
<td>Excluded</td>
<td>25OHD, nmol/l</td>
<td>73.9 (76.2)</td>
<td>February-June</td>
<td>76.4 (48.0)</td>
<td>Yes (P &lt; 0.01)</td>
</tr>
</tbody>
</table>

*Parametric tests were used. NOS: Newcastle-Ottawa Scale score out of nine for bias. Units standardized using 2.5 nmol/l = 1 ng/ml for 25OHD and 2.4 pmol/l = 1 pg/ml for 1,25-D. Composite means and s.o.s were calculated where results were reported in subgroups. 25OHD: 25-hydroxyvitamin D; 1,25-D: 1,25-dihydroxyvitamin D.*
distributed variable; despite this, all but one study reported results using mean (S.D.).

25OHD levels were found to be significantly lower in AS than controls in 7 of 11 studies (Fig. 1). Two studies could not be meaningfully compared with the others in Fig. 1 and are not shown: the article by Hmamouchi et al. [18] reported a statistically significant difference in the proportion of inadequate 25OHD levels (<50 nmol/l) but did not provide summary statistics to describe the data. The study by Yazmalar et al. [32] was the only one to report median 25OHD levels. They found a statistically significant difference in median as well as proportion of 25OHD deficiency (<25 nmol/l) between AS and controls.

Four studies reported no difference in 25OHD between cases and controls. In three of these, parametric tests were used to compare 25OHD with risk of type 2 error [12, 13, 32].

1,25-D levels were found to be significantly lower in AS cases compared with controls in two studies [8, 14] (Fig. 2).

The two studies that reported no significant difference in 1,25-D both used parametric tests with risk of type 2 error [13, L. Muntean, personal communication]. The study by Franck et al. [13] reported higher 1,25-D levels in AS patients than in controls. This study involved 38 AS patients and 52 controls and no statistically significant difference in mean 1,25-D was observed. This may reflect the relatively small sample size studied. A further abstract by Muntean et al. [20] failed to detect any significant difference in 1,25-D between 44 AS patients and 39 controls despite observing significantly lower 25OHD levels. However, the study used parametric tests (L. Muntean, personal communication).

In addition, three studies measured 25OHD in AS cohorts and did not include control groups. Lee et al. [23] recruited 14 AS patients from private rheumatology clinics; half with very early disease and some patients related to each other. They reported a mean 25OHD of 155.8 nmol/l (S.D. 97), which is much higher than that reported in studies assessing vitamin D in general population samples [33]. Furthermore, the small cohort had normal ESR and undetectable TNF, which suggests very low disease activity, and results may not represent other AS cohorts. No comment was made on the use of DMARDs or anti-TNFs. Therefore it was not included in Fig. 1 or Table 1. The second cohort study by Arends et al. [22] used a larger sample size of 128 AS patients to explore associations between vitamin D and bone metabolism. They observed mean 25OHD levels of 61.4 nmol/l,
which is similar to those described in other established AS cohorts shown in Fig. 1. Braun-Moscovici et al. [24] described a study of 121 patients including RA, PsA and only 14 AS patients. However, all analyses used grouped data and therefore cannot be used in this review. They reported a mean 25OHD of 31.8 nmol/l (s.d. 17.3) and a median of 25 nmol/l for AS patients.

Correlation between vitamin D and markers of disease activity
Fifteen studies discussed correlation of 25OHD or 1,25-D with markers of disease activity. The studies by Teichmann et al. [21] and Braun-Moscovici et al. [24] assessed correlation using combined vitamin D levels with other conditions and were therefore excluded. The results of the remaining 13 studies are summarized in Table 2. Five of 11 studies found significant inverse correlations between 25OHD level and markers of disease activity [12, 18, 19, 27, 31].

The study by Erten et al. [31] was the only one to formally report calculation of power and sample size for the primary aim of studying 25OHD and disease activity. It also controlled for seasonal variation in vitamin D and reported significant correlations between 25OHD and ESR/CRP in a cohort of 48 AS patients. They did not observe any significant association with BASDAI.

Durmus et al. [12] used a strong study design with seasonal control and exclusion of vitamin D supplements. They also reported significant inverse correlations for several a priori markers of disease activity. No significant cut-off point was reported and it was not possible to determine optimum 25OHD levels associated with reduced disease activity.

The article by Hmamouchi et al. [18] reported significant inverse correlations between 25OHD and BASFI/BASDAI adjusted for age and gender. The abstract by Baykal et al. [19] reported that 25OHD significantly correlated with BASDAI, CRP and ESR but did not provide data to allow interpretation of the strength of the association.

The abstract by Hmamouchi et al. [27] on 653 axSpA patients reported that 25OHD had a significant inverse correlation with radiological sacroiliitis, AS Disease Activity Score using CRP (ASDAS-CRP) and BASMI after adjusting for season and ethnicity.

The remaining six studies reported no correlation between measures of disease activity and 25OHD: Yazmalar et al. [32] assessed 25OHD in 72 AS patients in both summer and winter. No correlation with BASDAI was observed and no data were presented on correlation with inflammatory markers. Similar results were reported for the 44 AS patients examined by Muntean et al. [20, L. Muntean, personal communication]. The other four studies by Arends [22], Mermerci-Baskan [15], Aguier [25] and Fazal [26] did not control for vitamin D supplement or seasonal variation; large seasonal changes could add noise to the data and reduce the risk of detecting a significant correlation. Of the above six studies that reported no correlation, four used parametric tests with risk of type 2 error [12, 25, 32, L. Muntean, personal communication]. There were only two studies of 1,25-D and markers of disease activity. Both were published by Lange et al. [8, 14] and reported significant inverse correlations between 1,25-D and BASDAI, ESR and CRP. Both studies had similar and strong study designs and reported virtually identical correlation coefficients and P-values.

Other studies
The case–control study by Obermayer-Pietsch et al. [16] conducted in 104 AS patients and 54 healthy controls explored whether polymorphisms of VDR were associated with AS. They did not identify any association between FokI and BsmI polymorphisms and AS disease susceptibility, severity or duration of disease. They also did not observe any significant difference in 25OHD between AS cases and controls.

The case–control study of DBP polymorphisms by Jung et al. [28] in 223 AS patients and 239 controls found no association with AS susceptibility. However, some polymorphisms were associated with differential risk in peripheral arthritis and uveitis. 25OHD levels were not assessed.

Teichmann et al. [21] found a significantly higher prevalence of subclinical intestinal inflammation (positive anti-tissue transglutaminase (anti-htTG) but negative biopsy for coeliac) in AS vs PsA patients (77.8% vs 22.2%, P = 0.001). Pooled AS and PsA data showed significantly lower 25OHD in anti-htTG-positive patients, whereas 1,25-D was not different [21]. The authors suggest that subclinical malabsorption may contribute to vitamin D deficiency in these patients. However, it is worth noting that diet fulfills only 10-20% of our vitamin D needs [33].

A mass spectrometry biomarker study identified the vitamin D metabolite 23(S),25(R)-25-hydroxyvitamin D-26,23-peroxylactone as significantly lower in 18 AS patients compared with controls. No differences in serum levels of 25OHD or 1,25-D were observed [29]. No comment was made on why this particular molecule was chosen or if there was potential case selection bias. The clinical significance for this difference in vitamin D metabolite levels between AS and healthy controls is unclear.

Discussion
This systematic review has highlighted that there is evidence that AS patients have lower 25OHD levels than healthy controls. Seven of 11 studies found significantly lower 25OHD in AS patients compared with controls. However, cross-sectional study design impairs our ability to infer causality. There was also evidence for an inverse association between measures of disease activity and 25OHD. Five of 11 studies reported this inverse relationship. However, there are caveats to the use of markers of disease activity, especially in the context of cross-sectional studies. For example, vitamin D deficiency can potentially cause pain, and this may increase subjective disease measures such as BASDAI. These measures should therefore be interpreted in combination. The majority of studies that report no difference in 25OHD or no correlation with markers of disease activity used statistical tests with a risk of type 2 error.
### TABLE 2
Comparative summary of studies assessing correlation between 25OHD and/or 1,25-D and markers of disease activity

<table>
<thead>
<tr>
<th>Study</th>
<th>AS sample size, n</th>
<th>Vitamin D supplement</th>
<th>Vitamin D metabolite</th>
<th>Control for seasonal variation</th>
<th>Significant correlation with markers of disease activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lange et al. [8]</td>
<td>58</td>
<td>Not excluded</td>
<td>NSAI, 21</td>
<td>Summer</td>
<td>Yes 1,25-D</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DMARDs, 17</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Biologic agent, 21</td>
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<tr>
<td>Lange et al. [14]</td>
<td>70</td>
<td>Not excluded</td>
<td>NSAI, 17</td>
<td>May—August</td>
<td>Yes 1,25-D</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DMARDs, 83</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Biologic agent, 83</td>
<td></td>
<td></td>
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<tr>
<td>Durmus et al. [12]</td>
<td>99</td>
<td>Excluded</td>
<td>No comment</td>
<td>June—August</td>
<td>Yes 25OHD</td>
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<tr>
<td>Erten et al. [17]</td>
<td>48</td>
<td>Not excluded</td>
<td>No comment</td>
<td>December—March</td>
<td>Yes 25OHD</td>
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<td></td>
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<tr>
<td>Hmamouchi et al. [18]</td>
<td>70</td>
<td>Not excluded</td>
<td>11</td>
<td>Summer</td>
<td>Yes 25OHD</td>
</tr>
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<tr>
<td>Mermerci Baskan et al. [15]</td>
<td>100</td>
<td>Not excluded</td>
<td>No comment</td>
<td>No</td>
<td>No 25OHD</td>
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<td></td>
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<tr>
<td>Arends et al. [22]</td>
<td>128</td>
<td>Not excluded</td>
<td>No comment</td>
<td>No</td>
<td>No 25OHD</td>
</tr>
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<tr>
<td>Yazmalar et al. [11]</td>
<td>72</td>
<td>Not excluded</td>
<td>No comment</td>
<td>Summer</td>
<td>No 25OHD</td>
</tr>
<tr>
<td>Abstract Baykal et al. [19]</td>
<td>40</td>
<td>Not excluded</td>
<td>No comment</td>
<td>Winter</td>
<td>No 25OHD</td>
</tr>
<tr>
<td>Abstract Muntean et al. [20]</td>
<td>44</td>
<td>Excluded</td>
<td>No comment</td>
<td>Feb—June</td>
<td>No 25OHD</td>
</tr>
<tr>
<td>Abstract Aguiar et al. [25]</td>
<td>43</td>
<td>Not excluded</td>
<td>No comment</td>
<td>No</td>
<td>No 25OHD</td>
</tr>
<tr>
<td>Abstract Hmamouchi et al. [27]</td>
<td>653</td>
<td>No comment</td>
<td>No comment</td>
<td>Analysis adjusted for season</td>
<td>Yes 25OHD</td>
</tr>
<tr>
<td>Abstract Fazal et al. [26]</td>
<td>70</td>
<td>No comment</td>
<td>No comment</td>
<td>No</td>
<td>No 25OHD</td>
</tr>
</tbody>
</table>

Parametric tests were used. ASQoL: AS Quality of Life Scale; MAF: Multidimensional Assessment of Fatigue; VAS: visual analogue scale; PGA: patient global assessment; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score using CRP; 25OHD: 25-hydroxyvitamin D; 1,25-D: 1,25-dihydroxyvitamin D; axSpA: axial spondyloarthritis.
Much heterogeneity was observed with regard to disease duration, severity, treatment and drugs affecting bone metabolism. In addition, formal control for seasonal variation was poor. There was a wide range of NOS scores for bias and scores were equally heterogeneous in studies that reported positive findings and those that did not. The majority of studies evaluated vitamin D as part of multiple outcomes in the context of bone metabolism. Multiple secondary analyses in a small study will lead to a risk of error.

The fact that studies were not completely in agreement was not unexpected. Vitamin D metabolites are difficult to study for several reasons. These include the variation in 25OHD levels with even brief exposure to UVB as well as the long half-life of 25OHD (~3 weeks). Therefore a snapshot measurement of 25OHD without adjustment for or awareness of the season of testing can influence levels markedly and introduce both bias and noise when assessing levels in cases and controls. In addition to seasonal variation, the latitude of the study setting is important, as this can influence UVB exposure, making comparisons between countries complex.

Studies identified in this literature search suggested that VDR and DBP polymorphisms were not observed to be associated with AS disease susceptibility [16, 28]. The effect of vitamin D concentration on these manifestations is unclear. The high prevalence of anti-HLA antibodies in AS patients raises concerns over a possible risk of malabsorption. This impaired absorption of dietary vitamin D could contribute to its deficiency [34], particularly in patients with reduced UVB exposure.

Vitamin D has known immunomodulatory properties. It has been suggested to correlate with disease activity in and affect the susceptibility of many autoimmune conditions, including mixed CTDs [35], SSc [36], Behçet’s disease [37], SLE [38] and RA [39]. We have highlighted some evidence that this may also be true in AS. However, it is difficult to determine causality, as all studies identified were cross-sectional. This is particularly pertinent for the association between measures of disease activity and functional impairment, as poor mobility may further reduce UVB exposure and cause vitamin D deficiency rather than vitamin D deficiency causing worse disease. Studies by Lange et al. [8, 14] attempted to control for this by recruiting physically active patients, but did not comment on sun exposure. No longitudinal studies were found at the time of this literature search. Therefore this review was unable to assess the role of vitamin D as an immunomodulator in AS.

The evidence for association between serum 1,25-D and AS disease susceptibility and severity was limited. 1,25-D is difficult to study because it has a much shorter half-life and circulates at lower concentrations (pg/ml). 1,25-D is largely a renal product and serum concentrations are influenced by many factors, including DBP, VDR and 1-alpha-hydroxylase. Immunomodulatory functions of 1,25-D are proposed to act via auto-/paracrine mechanisms that are unlikely dependent upon serum concentrations [7]. 25OHD is therefore a better candidate to study. Low substrate availability to extrarenal CP27B may affect local 1,25-D production.

It is also possible that vitamin D has an immunomodulatory effect not dictated by absolute serum values; e.g. it may depend on the magnitude of seasonal variation or low levels at certain times of the year. 1,25-D up-regulates the bactericidal molecule cathelicidin in macrophages, and serum 25OHD levels correlate with cathelicidin expression [40]. A reduced ability to clear intracellular infection due to vitamin D deficiency may have implications for the aetiology and/or pathophysiology of AS. It has been shown that Shigella down-regulate cathelicidin as a survival mechanism [41]; this may be the case for other intracellular pathogens too. It would be interesting to study 25OHD in reactive arthritis, where the infectious aetiology is more accepted.

Well-designed and well-executed studies are needed. Understanding whether 25OHD is a risk factor for disease susceptibility is important, as modification of levels may protect against disease development in at-risk individuals. If vitamin D deficiency is a predictor of more severe disease in AS, understanding this could lead to identification of new pathogenic mechanisms in AS as well as cost-effective therapy interventions.

Rheumatology key messages

- Vitamin D levels are lower in AS patients than in healthy controls, although well-designed studies are lacking.
- Vitamin D level is inversely correlated with several markers of AS disease activity.
- Longitudinal studies are needed to see if there is a causal association with disease activity in AS.

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Supplementary data

Supplementary data are available at Rheumatology Online.

References


