

The effect of vitamin D levels on the assessment of disease activity in rheumatoid arthritis

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Abstract Disease activity in rheumatoid arthritis (RA) is assessed by a combination of objective and subjective tests, combined to produce a disease activity score in 28 joints (DAS28). There is some evidence that RA disease activity, as assessed by DAS28, can be influenced by vitamin D levels. It is difficult to know whether this is due to a true immunomodulatory effect of vitamin D or a more subjective effect of low vitamin D on pain perception. We addressed this issue by comparing vitamin D levels with disease activity, analysing each component of the DAS28 score separately. We measured 25-hydroxy vitamin D levels in 176 outpatients with RA at two different centres and recorded a DAS28 score using an ESR checked at the same time. We calculated DAS28 both with and without the patient's rating of their symptoms on the visual analogue score (VAS) to assess the effect of VAS on DAS28. The vitamin D results were expressed as nanomole per litre with 50 nmol/l taken as the lower limit of normal. We calculated mean levels of vitamin D and undertook a multivariate regression analysis to assess correlations between vitamin D levels and DAS28

(and its individual components), corrected for centre, age and gender. The overall mean DAS28 score was 3.66 (SE±0.11) using all four criteria and 3.43 (SE±0.10) using just three criteria (omitting VAS). The mean vitamin D level was 39.42 nmol/l (SE±1.55). There was no significant correlation between vitamin D and DAS28 scores with or without the inclusion of VAS. However, there was a significant inverse relationship between vitamin D and VAS itself (coefficient=0.249, $p=0.013$). The mean DAS28 score was greater in vitamin D-deficient patients and this was explained by their higher VAS scores. Our data confirms that vitamin D deficiency is common in RA. This paper provides evidence that the VAS component, assessing patient perception of symptoms, is inversely related to vitamin D, with lower levels producing higher VAS values. Although there was no overall correlation between vitamin D levels and DAS28, patients may perceive themselves or be perceived by assessors as having responded less well to disease modification in the presence of vitamin D deficiency. This could have major implications for subsequent management, and clinicians need to be aware of the potential confounding effect of vitamin D deficiency in assessing RA disease activity using the full DAS28 tool.

Key messages Vitamin D deficiency can influence disease activity scores in rheumatoid arthritis.

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Introduction

Interest in the role of vitamin D in rheumatic disease has developed over the last decade since the first reports reporting reduced levels of vitamin D in rheumatoid arthritis (RA) [1]. Vitamin D intake was inversely associated with increased relative risks for developing RA in an American study [2], while in Europe, significant inverse correlations

were reported between vitamin D levels and the activity of articular disease in those with established RA independent of latitude [3]. Debate developed over whether vitamin D deficiency actually did [4] or did not [5] increase the risk of developing RA. As assays of vitamin D became cheaper and were incorporated into routine clinical assessment, clinicians became increasingly aware of the high prevalence of low levels of vitamin D in a variety of rheumatic diseases, including RA [6, 7].

Disease activity in RA is assessed by a combination of objective and subjective measures, combined to produce a disease activity score in 28 joints (DAS28). There is some evidence that RA disease activity, as assessed by DAS28, can be influenced by vitamin D levels [8]. However, these findings, although demonstrable at initial assessment in early RA, have been reported to disappear after 3 years of follow-up [9]. It is difficult to know whether this represents a true immunomodulatory effect of vitamin D, as has been proposed [10], or a more subjective effect of low vitamin D on symptom perception. We have addressed this question by comparing vitamin D levels with disease activity, analysing each component of the DAS28 score separately.

Methods

The study was conducted in the winter months between December and February 2011. We measured 25-hydroxy vitamin D levels in consecutive 176 outpatients meeting EULAR criteria for RA [11] at two different centres using identical immunoassay techniques. Patients were not selected on the basis of their symptoms. Both centres obtained full audit approval from their Trusts' Research and Development Departments for the collection and analysis of anonymised vitamin D levels and related demographic data. All patients had a DAS28 score performed and recorded using an ESR, which was performed together with vitamin D levels at the same time as the clinical assessment. We standardised the use of the ESR over CRP as it has been shown to be more consistent. We collected and recorded data on the numbers of tender and swollen joints (0–28) for each individual patient. We also recorded the visual analogue score (VAS) obtained for each patient on a scale of 0–100. VAS was calculated on patients' global assessment of general health as recommended by EULAR [12]. All patients had their anti-cyclic citrullinated peptide (CCP) antibody status assessed and plain radiographs of their hands performed.

We calculated DAS28 both with and without the patient's VAS score to assess the effect on VAS on the overall DAS28 score. The vitamin D results were expressed as nanomole per litre with 50 nmol/l taken as the lower limit of normal. Patients with levels at or under 20 nmol/l were classified as having vitamin D deficiency and those with values of

between 20 and 50 nmol/l were classified as being vitamin D insufficient [13].

We assessed the correlation between vitamin D levels and DAS28 for the whole group using multivariable regression modelling. A causal pathway model was constructed to test the hypothesis that lower vitamin D levels might be associated with poorer subjective general health as assessed by VAS. In this, the proposed relationship between vitamin D levels and VAS was modelled as potentially confounded by age, gender and swollen joint counts (SJC), the latter as a proxy for objective disease activity. Recruitment centre (Leeds/Gateshead) was included as a potential interaction term for the effect of vitamin D levels and for the effect of SJC. The interaction term was retained in the model only if it was statistically significant. Age and gender were retained in the model regardless of statistical significance. Model assumptions were checked graphically. Analyses were performed in Stata IC, version 11.

Results

There were no differences in the data from each of the two centres. Overall, 44 (25 %) of patients were male, and the group mean age was 64 years (22 to 89 years). Mean disease duration was 12 years (1–37 years). Anti-CCP antibody was present in 58 % of patients and erosions were detected on plain radiographs of hands in 38 %.

Vitamin D levels were found to be reduced in the majority of patients, with 31 (18 %) having deficiency and 88 (50 %) having insufficiency. The overall mean level of vitamin D was 39.42 nmol/l (SE±1.55).

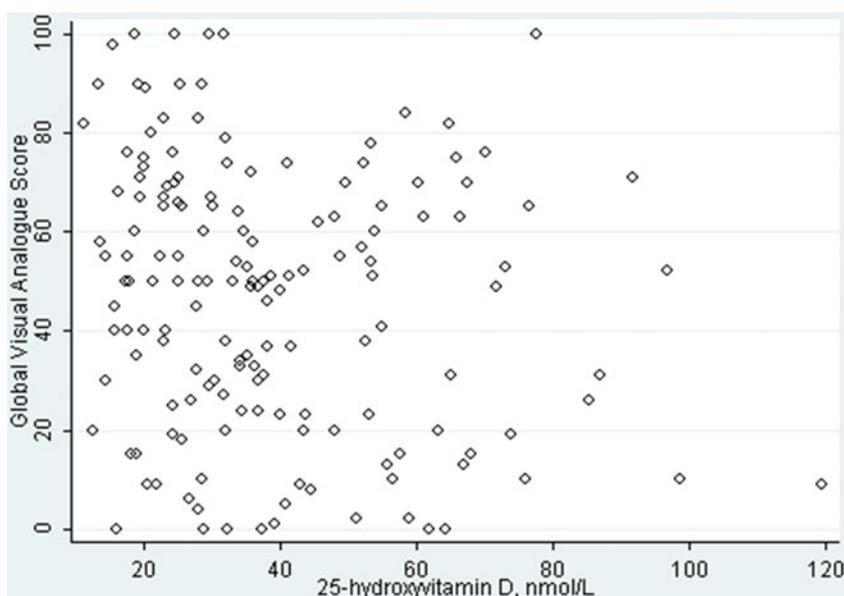
Mean values (SE) of the numbers of tender joints were 3.80±0.42 and swollen joints 2.35±0.21. The mean ESR value was 23.28±1.43. The mean VAS score was 45.31 (±1.98). The overall mean DAS28 score was 3.66 (SE±0.11) using all four criteria, and 3.43 (SE±0.10) using three criteria (with the omission of VAS).

As the centre interaction term was non-significant, it was removed from the model. The final model had four predictors: vitamin D, age, gender and SJC. The SJC was found to be strongly positively skewed and was therefore log-transformed. The overall *R*-squared value of the model was 0.1945, indicating that 19 % of the variance in VAS could be explained by the model.

There was no significant correlation between vitamin D and DAS28 scores with or without the inclusion of VAS. However, there was a significant correlation between VAS itself and vitamin D (coefficient 0.249, *p*=0.013) (Fig 1), while we found no significant correlation between VAS and either age or gender (Table 1).

There was a relationship between the level of vitamin D deficiency and the difference in DAS28 scores with and

Fig. 1 The significant relationship between vitamin D levels and visual analogue scores in the study population (coefficient=0.249, $p=0.013$)



without the inclusion of VAS. Those patients with vitamin D deficiency had a mean DAS28 score 0.38 higher when VAS was included, while the difference was less in those with vitamin D insufficiency at 0.25 and just 0.10 in those with adequate vitamin D levels. The difference in DAS28 scores with and without the inclusion of VAS between vitamin D-deficient and vitamin D-replete groups was significant ($p=0.023$) and is shown together with other comparisons between the patients grouped by vitamin D status in Table 2. There was no correlation between disease duration and vitamin D levels. Vitamin D supplements were offered to all patients with insufficiency or deficiency as identified in this study.

Discussion

Our data confirm that vitamin D deficiency is common in patients with established RA during the winter in northern England. Our patient population reflected the characteristics of a typical follow-up RA patient group, with a mean age of 64 years and an average disease duration of 12 years. Disease severity markers included a relatively high rate of CCP seropositivity but a lower percentage of patients with established erosive disease. Vitamin D levels were normal in just

one third of our RA population, and these figures are commensurate with other studies confirming seasonal variation with a marked reduction in vitamin D during winter months [3, 9].

A large meta-analysis has just confirmed that low vitamin D intake increases the risk of developing RA, and that vitamin D levels are inversely related to RA disease activity in most published series [14]. Although we found no overall correlation between vitamin D levels and disease activity in established disease, our data cannot provide evidence against such an effect in early RA. However, we have shown that patients’ subjective assessment of their general health does correlate inversely with vitamin D levels, suggesting that lower levels of vitamin D may indeed increase symptoms in established RA. Importantly, DAS28 scores were significantly increased in patients with vitamin D deficiency, and this was almost entirely explained by the inclusion of VAS. This effect was not seen in those with adequate vitamin D levels and persisted after correction for age and gender. A recent paper with smaller numbers of RA patients also showed a relationship between pain and vitamin D, although the authors did not examine individual components of the DAS28 score [15].

As expected, VAS showed a strong association with SJC. However, vitamin D levels significantly predicted VAS

Table 1 The coefficients for each predictor in the model with outcome as visual analogue score for patient global health

Predictor	Coefficient (95 % CI)	<i>p</i> value
25-Hydroxyvitamin D, nmol/l	-0.249 (-0.444, -0.054)	0.013
Age (completed years)	-0.309 (-0.630, 0.011)	0.058
Gender (female coded as 0, male coded as 1)	2.045 (-7.296, 11.385)	0.666
Swollen 28 joint count, log-transformed	12.433 (7.558, 17.309)	<0.001
Constant	63.872 (42.086, 85.657)	n/a

Table 2 Differences between groups based on vitamin D status

Variable	Vitamin D deficient	Vitamin D insufficient	Vitamin D replete
Number	31	88	57
Mean age (years)	57*	68	67
Mean VAS	53*	44	44
Mean DAS28 (4) (SE)	3.91* (0.16)	3.66 (0.13)	3.52 (0.14)
Mean increase in DAS28 with VAS	0.38*	0.25	0.10

Vitamin D deficiency = levels <20 nmol/l; vitamin D insufficiency = levels 20–50 nmol/l

* $p > 0.05$, for comparisons between vitamin D-deficient and vitamin D-replete groups

independent of SJC. With this model, an improvement in vitamin D levels by 50 nmol/l (a typical increase in vitamin D levels associated with treatment of vitamin D deficiency) would be associated with a 12.5 (95 % CI 2.7, 22.2)mm improvement in VAS. This is equivalent to an improvement of 0.17 (95 % CI 0.04, 0.31) points in the DAS28 composite score. In context, the UK NICE guidelines state that the DAS28 is required to improve by 1.2 points to class as an “adequate” response to therapy. Thus, treatment of vitamin D deficiency could account for 15 % (95 % CI 3, 26 %) of an “adequate” response to therapy. When assessing response to therapy, clinicians should be aware that treatment of vitamin D deficiency may be associated with an improvement in VAS that may have a substantive effect on the DAS28 score, independent of the swollen joint count.

We routinely supplemented patients with vitamin D deficiency with intramuscular vitamin D or oral ergocalciferol. Levels may take up to 4 months to normalise following such treatment. No formal study of the effect of supplementation on disease activity has been performed to gauge efficacy, although there is randomised controlled data to suggest that vitamin D supplementation improves pain in RA assessed by VAS within 3 months [16]. It would be interesting to repeat our study following vitamin D supplementation to assess whether this abolished the effects we have reported.

Our study included patients with a very variable disease duration. Although, no correlation between disease duration and vitamin D levels was evident, our patient population had reasonably well-controlled RA overall. In patients with early uncontrolled disease activity, the influence of vitamin D deficiency may differ. Due to the small sample size, there is considerable uncertainty in the effect size. Of note, we only measured 25-hydroxyvitamin D rather than the active metabolite 1,25-hydroxyvitamin D. Thus, the effect size quoted here may in fact represent an underestimate of the possible effect of adequate vitamin D supplementation. We did not collect data on parathyroid hormone levels or other

proxy measures of functional vitamin D deficiency but this may be an avenue for future research.

Our findings are of great potential relevance to clinicians as patients may be assessed as failing to respond adequately to disease modification in the presence of vitamin D deficiency. This might have major implications for subsequent management, as they may then be subjected to treatment escalation in spite of the absence of any ongoing disease activity. This carries implications at both clinical and financial levels. Hence, clinicians need to be aware of the potential confounding effect of vitamin D deficiency in the assessment of RA disease activity using the full DAS28 tool and should consider the measurement of vitamin D levels in their RA patients, especially where the assessment of the subjective components of the DAS28 appear to indicate greater disease activity than those which are more objective. It remains uncertain as to whether replacement of vitamin D, in those patients who exhibit deficiency, improves patients' VAS scores and thus reduces or removes this potential confounder.

Disclosures None.

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