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Relationships among vitamin D, disease activity, pain and disability in rheumatoid arthritis

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ABSTRACT

Background and objectives. *Vitamin D is a steroid hormone with important skeletal and non-skeletal biologic functions. Vitamin D deficiency is common and manifests with musculoskeletal symptoms. In rheumatoid arthritis (RA), vitamin D deficiency may be associated with increased disease activity and disability. We aimed to estimate the relationship between Vitamin D level and disease activity, pain, and disability in RA.*

Methods. *Data were drawn from 62 RA patients seen in an academic arthritis clinic. 25(OH)D levels were evaluated along with markers of RA disease activity, physician and patient global assessments, pain (VAS) and HAQ. DAS-28 was calculated. Vitamin D deficiency was defined as 25(OH)D levels <30ng/ml.*

Results. *Sixty-one percent of RA patients were classified as vitamin D deficient. In patients with active RA (DAS 28 score ≥2.6), 25(OH)D was moderately and inversely associated with DAS 28 (-0.38), pain (-0.49) and HAQ (-0.54) (p<0.01). However, no significant associations were found between 25(OH)D and these variables in patients in remission (DAS 28 <2.6). Vitamin D deficient patients with active RA had six times the odds (OR=6.0, 95% CI 1.2-31.2) of being moderately or severely disabled (HAQ≥1.25).*

Conclusion. *Vitamin D deficiency was common in this RA group. In patients with moderate to high disease activity, vitamin D deficiency was associated with higher DAS scores, pain and disability. Clinicians in northern climates may wish to monitor vitamin D status in their RA patients.*

Introduction

Vitamin D deficiency affects between 32% to 70% of the general population in North America (1, 2). Risk of vitamin D deficiency is greater at northern latitudes and in winter and spring (3).

Emerging evidence suggests that vitamin D plays an important role in immune regulation. Vitamin D receptors are found on several immune cells (4). *In vitro* studies have shown that vitamin D metabolite modulates T cell proliferation and dendritic cell function (5). Epidemiological data also imply that vitamin D deficiency may be a risk for development of autoimmune and other chronic diseases (3, 6).

Preliminary studies suggest that low levels of vitamin D may be common in rheumatoid arthritis (RA) (7, 8). Patel *et al*. (9) reported an inverse relationship between vitamin D levels and disease activity and disability in patients with early inflammatory polyarthritis. The goal of this study was to assess the prevalence of vitamin D deficiency in a sample of RA patients and to estimate relationships between vitamin D levels and disease activity, pain, and disability. We hypothesised that low levels of vitamin D would be common and inversely related to disease activity, pain, and disability.

Methods

Sample

Data are drawn from sixty-two consecutive patients whose vitamin D status was assessed during a routine clinic visit at the Johns Hopkins Arthritis Clinic from December 2003 through November 2006. All patients fulfilled ACR criteria for RA. This study was approved by the Johns Hopkins Internal Review Board. Baltimore MD is located at 39° latitude

Measures

Clinical measures of disease activity including tender and swollen joint counts, CRP and rheumatologist and patient global assessments were available in most cases. DAS-28 CRP scores were calculated for patients with complete data (10, 11). Pain was assessed with a 100 mm-visual analogue scale. Patients also completed the Health Assessment Questionnaire (HAQ)(12).

Vitamin D status was assessed by measuring serum 25(OH)D levels using standardised methods at accredited clinical laboratories (Quest and Labcorp). Vitamin D deficiency was defined as 25(OH)D level <30ng/ml, in accordance with expert consensus (13). Almost all patients (85%) had blood drawn on the day of the clinic visit; 15% had blood drawn within ±22 days of the visit. Patient information was obtained from the medical chart.

Statistical analysis

Variables were examined and transformed as needed to approximate a normal distribution. Frequencies were calculated for categorical variables, and means and standard deviations for continuous variables.

Using recommended cut points, RA patients were classified as being in remission (DAS-28 <2.6; n=15) or having active disease (DAS28 ≥2.6; n=31). All data needed to calculate DAS-28 scores were not available in 17 persons; we analysed these individuals separately. Pearson correlation coefficients were used to assess relationships between 25(OH)D levels and markers of disease activity and disability. Multivariable linear regression was used to estimate the independent contribution of 25(OH)D to disability after controlling for covariates and potential confounders.

Results

Patient characteristics

The sample was mostly female (82%) and white (82%) with a mean (SD) age of 57.6 (12.9) yrs and disease duration of 11.6 (12.3) yrs. Table I shows patient and RA-related characteristics by disease activity status. Groups did not differ significantly by sex, race/ethnicity or disease duration; individuals with active disease were older and had higher markers of disease activity.

Vitamin D status

The mean 25(OH)D of the sample was 33.86 (10.74) ng/ml (range 5.66 to 61.32 ng/ml). Overall, 38 of 62 (61.3%) were classified as vitamin D deficient (25(OH)D <30ng/ml). There was no significant difference (p=0.14) in vitamin D deficiency across seasons; Jan-Mar (70%), Apr-Jun (73%), Jul-Sept (52%), and Oct-Dec (61%). 25(OH)D levels were not associated with age (r=-.026; p=0.922), sex (25.91±9.78 *vs*. 28.35±14.09 for males *vs*. females; p=0.588) or disease duration (r=0.096; p=0.733), although there was a trend for minority patients to have lower levels (21.64 *vs*. 29.26 ng/ml for minority *vs*. white; p=0.087). The three RA subgroups did not significantly differ in their mean 25(OH)D levels (p=0.97) or by the proportion classified as vitamin D deficient (p=0.66) (Table I).

Table I. Selected patient characteristics and vitamin D status by disease activity level.

Variable	DAS<2.6 (Remission) n=15	DAS ≥2.6 (Active) n=31	DAS Unavailable (n=16)
Age (yrs)	51.4 ± 11.7[a]	60.8 ± 10.2[b]	57.2 ± 16.3[ab]
% Female	100	80	71
% Minority	0	17	18
Disease characteristics			
Disease duration (yrs)	11 ± 9	12 ± 15	9 ± 8
Tender joints	0.4 ± 0.7[b]	8.3 ± 7.1[b]	7.6 ± 9.6[a]
Swollen joints	1.5 ± 1.8[a]	9.4 ± 9.1[b]	2.5 ± 1.5[a]
DAS28-CRP	1.8 ± 0.4[a]	4.1 ± 0.8[b]	--
Pain (100 mm VAS)	15.3 ± 13.6[a]	44.8 ± 24.9[b]	57.3 ± 24.6[c†]
HAQ Score	0.4 ± 0.6[a]	1.2 ± 0.7[b]	1.5 ± 0.8[c]
Vitamin D status			
25(OH)D (ng/ml)	28.27 ± 14.16	28.10 ± 14.74	27.23 ± 10.34
Range (ng/ml)	8 – 51	6 – 86	14 – 53
<30 ng/ml (%)	53	58	69

Values are the mean ± SD unless otherwise indicated. Significant differences between groups are indicated by differing superscripts. [†]p<0.09 between Active and DAS Unavailable groups.

Table II. Unadjusted associations between 25(OH)D level, DAS28 scores, pain and disability among three groups of rheumatoid arthritis patients.

Variable	DAS <2.6 (Remission)	DAS ≥2.6 (Active)	DAS Unavailable
Disease activity			
C-reactive protein (mg/dl)	-0.402 (0.137)	-0.134 (0.481)	--
DAS-28	-0.272 (0.326)	**-0.379 (0.039)**	--
Pain	-0.201 (0.472)	**-0.485 (0.009)**	0.413 (0.126)
Tender joints (48)	0.331 (0.228)	**-0.354 (0.055)**	-0.268 (0.425)
Swollen joints (48)	-0.194 (0.488)	-0.242 (0.197)	-0.249 (0.461)
Global assessment			
Physician	-0.453 (0.120)	-0.236 (0.227)	0.449 (0.225)
Patient	0.190 (0.498)	0.288 (0.137)	-0.148 (0.584)
Disability			
HAQ	-0.086 (0.760)	**-0.536 (0.003)**	0.018 (0.948)

Values are the correlation coefficient and p-value.

Vitamin D, pain and disease activity

Among patients in remission and with unknown disease activity, no consistent relationships were found between 25(OH)D levels and DAS scores, joint counts, physician or patient assessments or pain (Table II) in bivariate analyses. However, in patients with active disease, 25(OH)D levels were moderately and inversely associated with DAS-28, pain, and tender joint counts, though not with swollen joint counts, physician or patient assessments.

Vitamin D and disability

No consistent relationship was evident between 25(OH)D levels and HAQ scores in patients in remission or with unknown DAS scores. However, 25(OH)D levels in patients with active RA were moderately and inversely associated with HAQ scores (Table II).

In multivariate analyses of active RA patients, we found that after controlling for age, race and DAS, 25(OH)D level had an inverse independent effect on HAQ scores ($F(4, 24)$=2.985, p=0.039). In this group, vitamin D deficient patients had six times the odds (OR= 6.0, 95% CI 1.2–31.2) of having a HAQ score ≥1.25 compared to the vitamin D sufficient patients.

We repeated these analyses including the 16 persons for whom DAS scores were unavailable, using tender joint

counts as an indicator of disease activity. Nine were classified as active (≥5) and 1 in remission (≤2). (Joint counts were not recorded for the remaining 7 persons.) We obtained essentially the same results when these individuals also were included in the analyses (data not shown).

Discussion

Our findings suggest that vitamin D deficiency is common in RA patients in the mid-Atlantic region throughout the year. Over 60% had vitamin D levels below the currently accepted, though conservative threshold of sufficiency (*i.e.* 30ng/ml). Others have also reported high prevalence rates of vitamin D deficiency in RA (7). Kroger *et al.* (8) reported that in Finland, 63% of 143 women with RA were below seasonally-adjusted norms.

When we initially evaluated relationships between vitamin D and variables of interest in the entire sample, no significant associations were evident (data not shown). In patients with active RA, however, we observed a moderate inverse relationship between vitamin D levels, DAS-28 scores and tender joint count. No such relationship was evident in the remission group. In contrast, Cutolo *et al.* (14) and Patel (9) reported an inverse association between DAS 28 and vitamin D levels in their entire sample, perhaps due to their larger sample size (n=118 and 206, respectively). There are other possible explanations for our findings. In our remission group, levels of pain and disability were low overall; one third reported no pain and 40% reported no disability. Conversely, in the group with active RA, one person reported no pain or disability. Even in the active RA group, the mean DAS score was only 4.1 (0.8), indicating relatively moderate disease activity. Thus, floor effects may have been a factor with the full sample. It also may be that vitamin D does not have detectable effects on disease activity and disability when RA is relatively quiescent.

In active RA, low vitamin D also was associated with pain and moderate-severe disability (*e.g.* HAQ >1.25). Patel *et al.* (9) reported similar results at baseline and one year later. In our study, vitamin D level was an independent predictor of greater disability in persons with active RA, even after controlling for age, race and disease activity. Vitamin D deficient patients had six times the odds of needing assistance with activities of daily living (*i.e.* HAQ≥1.25).

These preliminary data suggest that in active RA, vitamin D may play an independent role in the expression of disease activity, pain and disability. Mechanisms through which vitamin D may have an impact on active RA are unclear.

This was a hypothesis generating study; results must be considered to be preliminary. Our sample size was small and representative of RA patients seen in academic arthritis clinics. The cross-sectional design precludes inferences about causality. Thus, we are not able to determine whether vitamin D deficiency directly impacts RA symptoms and disability or whether the reverse may be true. Additional information including use of vitamin D agonists, associations with BMI, osteoporosis and osteoporotic fractures would have been desirable.

In conclusion, vitamin D deficiency appears to be common in RA and may be associated with increased disease activity, pain and disability in patients with active disease. Larger prospective cohort and interventional studies are required to replicate these findings and explore the direction of these relationships. Importantly, vitamin D deficiency is easily repleted in most individuals with intensive therapy (15). Given the evidence regarding the role of vitamin D in overall health, clinicians in northern climates should consider screening RA patients to identify and address suboptimal vitamin D levels.

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