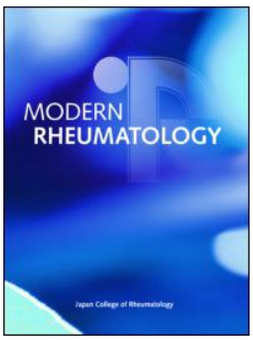

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Rapid Communication

An exploratory study on the role of vitamin D supplementation in improving pain and disease activity in rheumatoid arthritis

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Keywords

Rheumatoid Arthritis, Vitamin D, Pain, Disease Activity

Introduction

Rheumatoid Arthritis (RA) is characterized by systemic features and articular inflammation due to genetic and environmental factors. One of the possible relevant factor in the pathogenesis of RA might be Vitamin D[1]. Vitamin D receptors are nearly ubiquitous in the human tissue[2]. The association between low levels of serum 25-hydroxyvitamin D (25OHD) and disease activity in RA has been largely investigated since today[3]; a recent meta-analysis on more than 20 reports and more than 2000 patients with RA demonstrated a significantly positive association between lower 25OHD serum levels and higher disease activity[3]. Moreover recent studies showed that patients with long-standing RA develop central sensitization[4] with eventually self-sustaining neuropathic pain[5]. Low 25OHD serum levels are strictly associated with pain[6], and in particular with neuropathic pain in RA[6]. Vitamin D supplementation seems to improve neuropathic pain in patients with type 2 diabetes[7]. The cause-effect relationship between Vitamin D deficiency and disease activity or pain is not entirely clear[8]. Indeed, low 25OHD serum levels could be the consequence, and not the cause, of high disease activity or pain in RA. Interventional studies with Vitamin D supplementation might contribute to clarify this relationship. Currently the few available studies of this kind failed to demonstrate a clear benefit of Vitamin D on RA activity and a recent meta-analysis concluded that Vitamin D could only possibly reduce RA recurrence[9]. However, there were important limitations and bias in the latter study, like variable doses and baseline status of vitamin D, and so many doubts remain. Given this lack of knowledge our study aims to investigate the effects of the supplementation with cholecalciferol (vitD3) in improving pain and disease activity in RA patients with or without vitamin D deficiency (25OHD < 20 ng/ml).

Materials and methods

Patients The Study Group on Osteoporosis and Metabolic Skeletal Diseases of the Italian Society of Rheumatology (SIR) consecutively enrolled patients 18 years of age or older, from April 2015 through June 2015, with diagnosis of RA based on the ACR/EULAR 2010 classification criteria[10] with active disease (Disease Activity Score 28 joints C-Reactive Protein, DAS28-CRP > 2,6), on disease-modifying antirheumatic drugs therapy, and whose treatment was not expected to be changed over a 3-month period. All the patients, who were not in treatment with vitamin D, were supplemented with oral monthly 100,000 UI of VitD3. Additional excluding criteria were relevant renal, liver, endocrine, heart and bone metabolic diseases. The study was performed according to the Helsinki declaration and approved by local Ethic Committee on the 7th of July 2014

and accepted by the Italian drug agency. All patients provided written informed consent for their participation to the study.

Evaluation of RA activity The activity of RA was evaluated by skilled rheumatologists with DAS28-CRP, a composite score, collecting swollen joints, tender joints, CRP and patient general health (PtGH). Additionally, we specifically measured patient's pain intensity with a Visual Analog Scale (VAS).

Serum analysis Serum samples were collected in the morning after fasting at baseline and after 3 months and stored at -80 °C until they were assayed for 25OHD. Serum 25OHD was measured by ELISA (IDS Ltd. Boldon, UK) with intra-assay variabilities of 3% and inter-assay variabilities of 6%. All samples were measured in a single batch in order to limit inter-assay variability.

Statistical Analysis Data are presented as means ± standard deviation. Results were analysed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Data prior to and after VitD3 administration were compared using paired samples *t* test. Comparisons between two independent groups were performed by independent sample *t* test. A value of $p \leq 0.05$ was regarded as significant in all analyses.

Results

61 patients (47 females), with an average age ± SD of 58 ± 12 years within 26–86 years range with a mean disease duration of 82.2 ± 63.3 months were included. Main clinical characteristics are shown in Table I. At baseline the mean ± SD 25OHD levels were 22 ± 10 ng/mL. 43% of the patients were found to have vitamin D deficiency (<20 ng/mL). Mean serum 25OHD levels improved from 13 ± 5 to 32 ± 12 and from 29 ± 7 to 41 ± 10 ng/mL in patients with or without vitamin D deficiency at baseline, respectively. Mean VAS pain at baseline was 5.8 ± 2.2; it was significantly higher in patients with vitamin D deficiency than in patients without vitamin D deficiency (6.8 vs 4.9), respectively). Mean VAS pain improved in the all population from 5.8 to 4.8 ± 2.3 (p NS), but when we analysed subgroups on the basis of baseline vitamin D status (cut-off 20 ng/mL) we found that VAS pain significantly decreased from 6.8 ± 1.9 to 5.4 ± 2.0 ($p < 0.01$) only in the patients with vitamin D deficiency at baseline (Fig. 1). Mean DAS28-CRP at baseline was 3.8 ± 0.9, with a significantly negative correlation with 25OHD serum levels at baseline ($r = 0.237$, $p < 0.05$). A trend of DAS28-CRP to decrease was seen at 3 months to 3.2 ± 1.2 (p NS). On the contrary, when subgroups were made on the basis of vitamin D baseline status a significant decrease was seen only for patient with vitamin D sufficiency (≥20 ng/mL) from 3.7 ± 0.7 to 2.9 ± 1.0 (Fig. 1). We further analysed each component of DAS28-CRP and, accordingly to previous shown results, we found a statistically significant decrease in 2 out of 4 of the DAS28-CRP items only in

patients with 25OHD levels higher than 20 ng/ml. Tender joints and patients' global health decrease respectively by a mean of 2.7 ± 4.0 ($p < 0.001$) and 0.9 ± 1.6 ($p < 0.001$); swollen joint almost reach statistically significance with a mean decrease of 0.7 ± 2.1 (p 0.07). Regarding patients with baseline 25OHD levels below 20 ng/ml we do not find any significant change in any item of DAS28-CRP.

Discussion

Our study suggests that Vitamin D might have different effects on disease activity and pain in patients with RA, depending on the baseline serum levels of 25OHD. Our results show that supplementation of patients without Vitamin D deficiency seems to be associated to an improvement on DAS28-CRP. Conversely, supplemented patients with vitamin D deficiency at baseline has no improvement on DAS28-CRP but a significant improvement on pain. Currently the major concern is if the Vitamin D effect on disease activity scores is due to a true effect on inflammatory cytokines or a more subjective effect of Vitamin D on pain[11]. As a matter of fact, the role of vitamin D in chronic inflammatory painful diseases might be double. Firstly, Vitamin D has proved to reduce circulation inflammatory cytokines in RA[12, 13]. Secondly, neuropathic pain, that is commonly present in RA, especially in long-standing disease, seems to be favourably affected by Vitamin D[14]. Yesil and colleagues recently reported the association between Vitamin D levels and neuropathic pain in RA[6]. According to this study the prevalence of neuropathic pain was 5.8 times higher among patients with serum Vitamin D levels below 20 ng/mL, with significant negative correlation between a neuropathic pain score and Vitamin D levels ($r = -0.444$, $p = 0.01$). Vitamin D is considered active in the brain and is considered a neuroactive substance and could also stimulate the production of nerve growth factor with eventually a neuroprotective effect[15]. Almost all the disease activity score used to assess RA comprehend patient reported global health or pain, with, most of the time, numerical rating scale or VAS. Pain assessed with these scales is heavily affected by the previous pain experiences and by the possible presence of neuropathic pain, both these conditions are definitely not related to the actual inflammatory status. DAS28-CRP not specifically includes pain assessment but better characterizes the inflammatory status of patients; on the other side VAS for pain specifically address the pain status without giving information about inflammation. On the basis of our observations we could then speculate that vitamin D deficiency in RA patients is mainly characterized by neuropathic pain and that the main effect on disease activity of Vitamin D supplementation in this condition is the improve in pain. Over 25OHD serum levels of 20 ng/ml we can speculate that Vitamin D supplementation might have effects on the immune system. Supporting the latter result we founded a significant correlation between baseline values of vitamin D

and DAS28-CRP in our cohort of long standing RA patients. Indeed, our results are in line with previously published results showing that supplementation of vitamin D in RA patients with long standing and persisting disease activity contributed to significant improvement in disease activity[16].

The present study does have strength and limitations. The main strength is the longitudinal design of the study, limitations are due to small number of patients included and the short follow-up. The small number is due to recruiting patients in the same period of the year (from April to June), limiting seasonal variation of 25OHD serum levels. Moreover, the present study was not conducted versus placebo for ethical reasons and Vitamin D was administered in bolus for practical reasons and maybe we could expect different results with daily administration. In conclusion VitD3 supplementation appears to be associated with significant and different effects on pain and disease activity in RA patients depending on 25OHD serum levels. Vitamin D deficiency (<20 ng/mL) seems to be mainly correlated with pain, while higher serum levels of 25OHD might have effects on the immune system. The exact mechanism that might explain the dual effect of vitamin D is still not known precisely and a randomized, double-blind, low versus high vitD3 dose or placebo-controlled trial is recommended.

Conflict of interest

None.

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Table I. Main clinical characteristics of the study population at baseline: number (percentage) or mean ± standard deviation (SD)

Gender	**All patients**	**Baseline Vitamin D < 20 ng/ml**	**Baseline Vitamin D ≥ 20 ng/ml**
Male	14 (23%)	4 (15%)	10 (28%)
Female	47 (77%)	22 (85%)	25 (72%)
Age in years (range)	58 ± 12	58 ± 11	58 ± 13
Disease duration in months (range)	82.2 ± 63.3	85.2 ± 65.2	80.6 ± 62.8
CRP mg/L	3.5 ± 6.2	3.3 ± 8.2	3.5 ± 4.3
DAS28 CRP	3.8 ± 0.9	3.9 ± 1.1	3.7 ± 0.7
Tender Joints (0-28)	6.6 ± 4.7	7.6 ± 5.1	5.7 ± 4.3
Swollen Joints (0-28)	2.8 ± 3.5	3.4 ± 4.3	2.3 ± 2.5
Patient's Global Health (0-10)	5.7 ± 1.5	5.9 ± 1.9	5.6 ± 1.0
VAS Pain (0-10)	5.8 ± 2.2	6.8 ± 1.9	4.9 ± 2.0
Serum 25 OH Vitamin D ng/mL	22.1 ± 10.0	12. 6 ± 4.7	28.5 ± 6.8
≥20 ng/mL	35 (57%)	0	35 (100%)
<20 ng/mL	26 (43%)	26 (100%)	0
DMARDs taking			
Hydroxychloroquine	5 (8.2%)	2 (7.7%)	3 (8.5%)
Methotrexate	40 (65.5%)	16 (61.5%)	24 (68.5%)
Leflunomide	6 (9.8%)	2 (7.7%)	4 (11.5%)
Biologic treatment	10 (16.5%)	6 (23.1%)	4 (11.5%)
Glucocorticoid			
Taking	33 (54%)	15 (57%)	18 (51%)
Not taking	28 (46%)	11 (43%)	17 (49%)

Figure legend

Fig 1. DAS28 CRP and VAS PAIN changes in patients with or without baseline vitamin D deficiency