

Is cholecalciferol a potential disease-modifying anti-rheumatic drug for the management of rheumatoid arthritis?

M. Bellan^{1,3}, L. Andreoli⁴, A. Nerviani^{3,5}, S. Piantoni⁴, G.C. Avanzi^{1,6},
D. Soddu^{1,2}, E. Hayden^{1,2}, M. Pirisi^{1,3}, P.P. Sainaghi^{1,3}

¹Department of Translational Medicine, Università del Piemonte Orientale UPO, Novara, Italy;

²Division of Internal Medicine, Immunorheumatology Unit, CAAD (Center for Translational Research on Autoimmune and Allergic Disease) "Maggiore della Carità" Hospital, Novara, Italy;

³IRCAD, Interdisciplinary Research Center of Autoimmune Diseases, Novara, Italy;

⁴Rheumatology and Clinical Immunology Unit and Department of Clinical and Experimental Sciences, Spedali Civili and University of Brescia, Italy;

⁵Centre for Experimental Medicine and Rheumatology, Barts and The London School of Medicine and Dentistry, William Harvey Research Institute, Queen Mary University of London, United Kingdom;

⁶Emergency Medicine Department, "Maggiore della Carità" Hospital, Novara.

Mattia Bellan, MD, PhD

Laura Andreoli, MD, PhD

Alessandra Nerviani, MD, PhD

Silvia Piantoni, MD

Gian Carlo Avanzi, MD

Daniele Soddu, MD

Eyal Hayden, MD

Mario Pirisi, MD

Pier Paolo Sainaghi, MD, PhD

Please address correspondence to:

Dr Mattia Bellan,

Department of Translational Medicine,
Università del Piemonte Orientale UPO,
via Solaroli 17,

28100 Novara (NO), Italy.

E-mail: mattia.bellan@med.uniupo.it

Received on February 23, 2019; accepted
in revised form on July 1, 2019.

Clin Exp Rheumatol 2020; 38: 343-349.

© Copyright CLINICAL AND

EXPERIMENTAL RHEUMATOLOGY 2020.

Key words: vitamin D,
cholecalciferol, rheumatoid arthritis,
anti-rheumatic agents

Competing interests: none declared.

ABSTRACT

Vitamin D is a pleiotropic molecule with a well-characterised immunomodulatory activity in vitro; however, its potential clinical application in autoimmune conditions has yet to be clarified. Several authors have investigated the use of vitamin D as a disease-modifying anti-rheumatic drug (DMARD) in rheumatoid arthritis (RA), obtaining divergent conclusions.

This systematic review summarises and critically analyses the findings of papers assessing the impact of vitamin D supplementation on pain relief, disease activity, functional status and flare rate. We conclude that the correction of hypovitaminosis D may have a beneficial effect on pain perception; moreover, the achievement of an adequate plasma vitamin D concentration obtained with high-dose regimens might evoke immunomodulatory activities of vitamin D and favourably impact on disease control. Nevertheless, the current evidence is still not strong enough to support the use of cholecalciferol as a DMARD in RA, and further studies are required to clarify this issue.

Introduction

Vitamin D is a fat-soluble hormone, which is mainly involved in the regulation of calcium/phosphate metabolism (1-3). In the last decades, the overwhelming evidence that vitamin D receptor (VDR) is expressed not only by cognate vitamin D targets but also by other cell types and tissues allowed several authors to postulate a broader role for vitamin D in human physiology than that already ascertained, *i.e.* the simple control of calcium/phosphate levels. The most convincing evidence in this sense has been obtained in the field of immunology. Firstly, the exposure to

activated vitamin D affects monocytes and macrophages by enhancing their phagocytic, mycobactericidal, and tumor-cell cytotoxic ability (4, 5), while at the same time limiting the production of crucial proinflammatory cytokines such as Interleukin 6 (IL-6) and tumour necrosis factor α (TNF- α) (6). Moreover, by down-regulating the expression of MHC II and costimulatory molecules, vitamin D suppresses antigen presentation and chemotactic capacity of monocytes and dendritic cells (DCs) (7, 8).

The immunomodulatory effects of vitamin D on the adaptive immune system are likewise substantial. On B cells, vitamin D acts by inhibiting their proliferation, differentiation, and immunoglobulin secretion (9); furthermore, it limits T cells cytotoxic activity (10) and drives the CD4⁺ differentiation towards the suppression of Th₁ and Th₁₇ subsets, while favouring the less inflammatory Th₂ or T_{reg} phenotype (11-13).

Remarkably, in the specific context of rheumatoid arthritis (RA), vitamin D can suppress the *in vitro* proliferation of synoviocytes isolated from synovial tissue of RA or osteoarthritis patients. The production of proinflammatory cytokines is synergistically reduced by dexamethasone and the vitamin D analogue, calcipotriol (14). These findings are in line with data from animal models. Indeed, synoviocytes derived from joints of rats with collagen-induced arthritis show a decrease in IL-1 β , IL-6, IL-8, and PGE₂ production and a reduction of MMP-3, INOS, and Cox-2 mRNA expression upon treatment with 1,25(OH)₂ vitamin D (15). Similarly, vitamin D downregulates the production of matrix metalloproteinase (MMP)-1, MMP-3, and MMP-9 in human IL-1 β -stimulated synoviocytes (16).

In line with these findings, it is reasonable to postulate a potential role for vitamin D as an immune-regulator in the management of RA (17, 18). First evidences in support to this hypothesis date back to more than 80 years ago. In 1935, Dreyer & Reed reported a clinical improvement of the disease with cholecalciferol 300000-500000 IU per day (19); similarly favourable observations confirmed these findings in the following years. Since the availability of a plethora of highly effective drugs has dramatically changed the natural history of RA in the last two decades, someone trying to translate those early data into current practice would be simply unreasonable. Besides, a new set of classification criteria and different scores for disease activity have been implemented. In brief, these remote studies cannot be considered more than a clue of the possible usefulness of vitamin D as a disease-modifying drug in RA. Nonetheless, the demonstration of the effectiveness of vitamin D add-on to the standard of care for RA control might provide a novel inexpensive and well-tolerated therapeutic tool. The present study aims to systematically review the current evidence supporting the potential use of vitamin D as a disease-modifying anti-rheumatic drug (DMARD) for the management of RA.

Methods

We performed a systematic review of the literature looking for studies evaluating the potential role of cholecalciferol as DMARD in RA. On 9th December 2018, we interrogated Pubmed using the following string: “Vitamin D AND Rheumatoid Arthritis”. This search yielded 691 publications of potential relevance.

We applied the following inclusion criteria:

- Full-text paper
- English language available
- Cohort study (prospective or retrospective), case-control study or randomised controlled trial
- The effect of vitamin D supplementation on different endpoints related to disease control in RA in human subjects

We applied the following exclusion criteria:

- Letters, case reports, reviews, abstracts
- Studies in which the effect of cholecalciferol on RA endpoints is not evaluated.

Retrieved studies were screened according to inclusion and exclusion criteria by two of us (M.B. and P.P.S.); 604 studies were excluded after the evaluation of the title, 74 after the revision of the abstract, and two after reading the full text. Reasons for exclusion were recorded and are detailed in Figure 1. Eleven studies were eventually selected.

The following data were extracted from each study deemed worthy of inclusion:

- First author’s surname, journal and year of publication
- Design
- Sample size
- Concomitant ongoing DMARDs treatment
- Vitamin D or vitamin D analogue regimen administered
- Endpoints
- Outcome(s)

The main findings of all the selected papers are described in Table I.

Results

Several of the studies included in this review evaluated the effect of vitamin D on pain relief in RA patients. At best, they suggest slight or moderate efficacy of cholecalciferol in reducing pain and improving subjective endpoints, independently of the regimen used (20, 21). Buondonno *et al.* found a non-significant trend ($p=0.096$) towards lower pain scores assessed by visual analogue scale (VAS) among patients treated with a single dose of cholecalciferol 300000 IU along with methotrexate (15 mg/week) and prednisone (2-4 mg/day) in comparison with placebo. However, the small sample size (21 patients in the treatment group *versus* 18 patients in the placebo group) might have precluded reaching statistical significance. In the same study, the authors demonstrated a significant improvement in the Global Health (GH) score at three months of patients treated with cholecalciferol (22). Con-

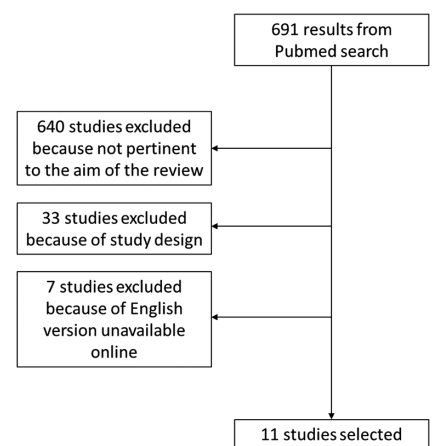


Fig. 1. Flowchart of the study selection process. In figure 1, we reported the flowchart representing the process of selection of the studies included in this systematic review.

versely, in one publication by Hansen *et al.*, the GH score was negatively affected by vitamin D supplementation. The limited number of patients (11 patients in the vitamin D group *versus* 11 patients in the control group), as well as the use of ergocalciferol rather than cholecalciferol, might explain this apparent discrepancy (23).

Furthermore, when objective measurements and ambitious outcomes such as inflammatory markers reduction or disease activity improvement were considered, findings were even less consistent. In 1973, Brohult and Jonson (20) documented significant subjective and objective clinical improvement as well as decrease in the erythrocyte sedimentation rate (ESR) in 25 patients treated with very large doses (100000 IU daily) of cholecalciferol in comparison with 25 placebo-controls. None of the patients included in this study was receiving DMARDs. More recently, the effects of cholecalciferol along with a concomitant DMARD treatment have been tested in a placebo-controlled trial (24). The supplementation with cholecalciferol 50000 IU/week did not increase significantly the proportion of patients whose disease activity score 28 (DAS 28) was improved at 12 weeks (24), yet a trend towards a better DAS28 in the treatment group and a negative correlation between 25(OH)vitamin D levels and DAS28 was observed. However, in this study: i. Patients were treated with variable DMARDs strategies; ii. Base-

Table I. Summary of review findings. The table reports the main findings of all the papers included in the present review.

Authors	Journal and year	Design of the trial	Patients	DMARD treatment	Cholecalciferol regimen	Endpoints	Main findings
Brohult <i>et al.</i> ²⁰	<i>Scand J Rheumatol</i> 1973	Double-blinded, randomised, placebo-controlled clinical trial	25 (study group) vs. 25 (control group)	None	Cholecalciferol 100000 IU/daily for 1 year	ESR reduction, objective and subjective improvement	Cholecalciferol group showed a significant objective and subjective improvement and a reduction of ESR
Andjelkovic <i>et al.</i> ²⁷	<i>Clin Exp Rheumatol</i> 1999	Open label trial	19 RA patients with active RA	MTX ± PDN	2 µg/day alphacalcidol for 3 months	Disease activity (measured by RAI, Lee index, tender and swollen joint)	Alphacalcidol improves disease activity
Gopinath <i>et al.</i> ²¹	<i>Int J Rheum Dis</i> 2011	Open-label Randomised Controlled Trial	59 (study arm) vs. 62 (control arm) early RA patients, DMARD naive	MTX + SSZ + HCQ + NSAIDs	calcium carbonate 1000 mg + cholecalciferol 500 IU/day for 3 months vs. calcium carbonate 1000 mg alone	Pain relief assessed by VAS score	Vitamin D supplementation in previously DMARD naive early RA patients significantly improves pain relief
Salesi <i>et al.</i> ²⁴	<i>Rheumatol Int</i> 2012	Double-blinded, randomised, placebo-controlled clinical trial	50 (study arm) vs. 48 (control arm) RA patients	MTX ± HCQ and/or PDN	Cholecalciferol 50000 IU/week for 12 weeks vs. placebo	Proportion of patients with a 0.6 and 1.2 improvement in DAS28	No significant improvement in vitamin D treated patients
Dehghan <i>et al.</i> ³⁰	<i>Z Rheumatol</i> 2013	Double-blinded, randomised, placebo-controlled clinical trial	40 (study arm) vs. 40 (control arm) RA patients in remission	MTX and/or HCQ ± PDN	Cholecalciferol 50000 IU/week for 6 months vs. placebo	Number of flares in patients in clinical remission	No statistical reduction in the number of flares or in prednisolone dose required
Hansen <i>et al.</i> ²³	<i>J Clin Rheumatol</i> 2014	Double-blinded, randomised, placebo-controlled clinical trial	11 (study arm) vs. 11 (control arm)	Mixed not specified	Ergocalciferol 50000 IU three times weekly for four weeks, then 50000 IU twice monthly for 11 months vs. placebo	DAS28, SF-36, HAQ, Patient's and Physician's GH	Vitamin D supplementation worsen SF-36 and patient's global assessment. No impact on DAS28
Yang <i>et al.</i> ²⁹	<i>Exp Ther Med</i> 2015	Randomised controlled open-label trial	168 (Normal vitamin D unsupplemented) vs. 84 (low vitamin D supplemented) vs. 88 (low vitamin D unsupplemented) RA patients in remission	Not specified	Alphacalcidol 0.25 µg/daily for 8 weeks	RA recurrence	The recurrence rate was significantly lower in normal vitamin D group vs. unsupplemented; a non-significant trend towards lower recurrence rate was shown for supplemented vs. unsupplemented arms
Chandrashekara <i>et al.</i> ²⁵	<i>Int J Rheum Dis</i> 2015	Randomised open label trial	73 with residual disease activity (DAS28ESR >2.6) and low vitamin D levels	MTX and/or LFN and/or HCQ	Cholecalciferol 60000 IU/week for 6 weeks then 60000 IU/month for 3 months	DAS28, VAS pain, TJC and SJC	The addition of vitamin D to the ongoing treatment improves disease activity measured as DAS28, TJC and SJC
Buondonno <i>et al.</i> ²²	<i>PlosONE</i> 2017	Double-blinded, randomised, placebo-controlled clinical trial	21 (study arm) vs. 18 (placebo arm) early RA patients	MTX + PDN	Single cholecalciferol 300000 IU dose vs. placebo	DAS28, CRP, ESR, VAS pain, GH, HAQ	Cholecalciferol improves GH at 3 months; no effect on other parameters
Soubrier <i>et al.</i> ²⁸	<i>Clin Exp Rheumatol</i> 2018	Double-blinded, randomised, placebo-controlled clinical trial	29 (study arm) vs. 30 (placebo arm) RA patients DAS28 >2.6	Stable DMARD regimen	Cholecalciferol 100000 IU single dose vs. placebo	HAQ, VAS pain, SF-36, DAS28, ESR, CRP	Cholecalciferol improves HAQ, ESR and CRP; no effect on the other parameters
Adami <i>et al.</i> ²⁶	<i>Mod Rheumatol</i> 2018	Open label trial	61 patients with active RA (DAS28 >2.6) on stable DMARD	Mixed regimen, stable during the trial	Cholecalciferol 100000 monthly for 3 months	VAS pain, DAS28-CRP	Correction of hypovitaminosis D improves pain; supplementation of patients without vitamin D deficiency in associated to an improvement on DAS28-CRP

RA: rheumatoid arthritis; DMARD: disease-modifying anti-rheumatic drug; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MTX: methotrexate; SSZ: sulfasalazine; HCQ: hydroxychloroquine; PDN: prednisone; NSAID: non-steroidal anti-inflammatory drugs; LFN: leflunomide; IU: international units; VAS: visual analogue scale; RAI: Ritchie articular index; SF-36: short form health survey; HAQ: Health Assessment Questionnaire; GH: global health assessment; TJC: tender joints count; SJC: swollen joints count.

line vitamin D levels were well above the lower normal limit both among patients assigned to active treatment and in controls, which is rather uncommon in RA patients; iii. Post-treatment increase of 25(OH) vitamin D concentration was minimal (107 vs. 125 nmol/L), suggesting suboptimal compliance and/or adequacy of the regimen used.

As mentioned above, Buondonno *et al.* showed an improvement in the patients' GH score but failed to demonstrate the additional advantage of a single loading dose of 300000 IU cholecalciferol on the disease activity (22).

In contrast, a recent open-label interventional study including RA patients with residual disease activity (DAS28 >2.6) reached substantially different conclusions. Indeed, adding cholecalciferol 60000 IU/week for six weeks followed by 60000/month to a stable DMARD treatment significantly increased the 25(OH)vitamin D levels measured at three months from 10.05 ng/ml (25.08 nmol/L) to 57.21 ng/ml (142.79 nmol/L). Importantly, this raise was mirrored by a significant decrease in the VAS pain, tender and swollen joints counts, and DAS28 (either calculated with ESR or CRP) (25).

A recent paper from the Study Group on Osteoporosis and Metabolic Skeletal Diseases of the Italian Society of Rheumatology (SIR) reached similar conclusions (26). None of the 61 patients studied were receiving vitamin D at the time of recruitment and all had active RA despite a stable dose of DMARD. They were given 100000 IU of cholecalciferol monthly over a three months period. The study population was split according to the baseline vitamin D level observed, using 20 ng/ml as the cut-off value to define vitamin D deficiency; mean serum 25(OH) vitamin D concentration improved from 13±5 to 32±12 ng/mL and from 29±7 to 41±10 ng/mL in patients with and without vitamin D deficiency (<20 ng/ml) at baseline, respectively. Overall, pain improved (with VAS decreasing from 5.8 to 4.8±2.3), but statistical significance was reached only in the vitamin D deficient group. Likewise, mean DAS28-CRP at three months decreased numerically but not significantly in the

population as a whole (from 3.8±0.9 to 3.2±1.2), but the observed improvement reached statistical significance in the vitamin D-deficient group.

A different vitamin D analogue, alfacalcidol (or 1-hydroxycholecalciferol), has been tested as potential DMARD in a study published in 1999 by Andjelkovic *et al.* These authors evaluated the effect of the add-on of 2 µg/day of alfacalcidol to methotrexate (10 mg/week) with or without concomitant prednisone (10 mg/day). After three months of alfacalcidol therapy, 89% of the patients had improved. A significant decrease in the number of swollen and tender joints was demonstrated in all RA patients, being paralleled by the improvement in both the Ritchie Articular Index and the Lee Index, and associated with a significant decline of ESR and CRP (27).

A recently published study also evaluated the effect of cholecalciferol supplementation on the functional status of patients with RA assessed by the Health Assessment Questionnaire (HAQ) (28). No significant differences between vitamin D- and placebo-treated groups were evident when the outcome was assessed without adjustments; however, adjusting for age, gender, season, and initial vitamin D status, the between-group difference in the HAQ score at six months achieved statistical significance (Vitamin D group -0.03±0.23 vs. 0.08±0.25 placebo group, $p=0.046$).

Finally, the effectiveness of vitamin D supplementation on the prevention of RA flares has been evaluated in two different studies. In 2015, Yang *et al.* demonstrated that RA patients in remission are at higher risk of disease relapse in the presence of a coexisting vitamin D deficiency, defined by 25(OH) vitamin D plasma concentration <30 ng/ml, in comparison to patients not vitamin D deficient. However, the correction of the low baseline levels of vitamin D by alfacalcidol supplementation (0.25 µg, twice a day) did not reduce the rate of recurrence as compared to the unsupplemented group (29). Similarly, Dehghan *et al.* failed to prove a protective role for cholecalciferol supplementation with regard to the risk of flares in RA patients (30).

It is relevant to note that the favourable safety profile of cholecalciferol-based regimens was confirmed in all the studies (above) in which they were used, independently of the dose. This did not hold true for alfacalcidol, whose highest dose was associated with an increased risk of asymptomatic hypercalciuria (27).

Discussion

Vitamin D is a pleiotropic molecule with well-characterised and consistently proven immunoregulatory activity *in vitro*, which to date has failed to translate into convincing efficacy in humans with dysregulated immunity.

Here, we have reviewed the current literature on the potential use of vitamin D as a DMARD in RA management, adopting a systematic approach. We do not think we can conclude either in favour or against a significant DMARD activity by vitamin D, since the results and conclusions of the studies we analysed were, to a large extent, divergent. Several reasons can explain the observed discrepancies, including:

- 1- Small sample size of interventional trials;
- 2- Enrolment of patients at diverse disease stages, with variable disease duration and multiple ongoing DMARD regimens;
- 3- Choice of different outcomes and endpoints;
- 4- Use of different molecules and dosages, with significant variation over the years.

Nevertheless, we do believe that some plausible considerations can be made on this topic.

First, to properly evaluate the effects of vitamin D supplementation in RA, it is worth to keep in mind that the mechanisms underlying pain and inflammation overlap only partially. Although inflammation is partially responsible for pain perception in RA, patients with a long-standing disease may develop central sensitisation (31) and neuropathic pain (32). In this context, vitamin D could play a relevant role, since hypovitaminosis D has been associated with neuropathic pain in RA (33). Therefore, the correction of vitamin D deficiency might reasonably

improve the neuropathic pain in RA, as already demonstrated in patients with type 2 diabetes mellitus (34, 35). There is substantial agreement on the efficacy of cholecalciferol supplementation to relieve pain, even at relatively low doses. In this context, the correction of hypovitaminosis D in RA patients is likely accompanied by the additional advantage of reducing pain, as supported by the observations of Adami *et al.* (26), who showed a beneficial effect on the VAS pain only in patients with a baseline vitamin D deficiency. In the presence of a satisfactory vitamin D status, the contribution of the hypovitaminosis D to neuropathic pain is probably negligible, thus explaining why it lacks efficacy.

Improvement of the disease activity implies a broader effect on objective parameters, such as inflammatory markers and joint involvement, which globally reflect the contribution of systemic inflammation. In the study mentioned above, a significant improvement of the DAS28-CRP was observed only among patients with higher vitamin D plasma levels, suggesting that the immunoregulatory activity of vitamin D probably requires greater 25(OH)vitamin D concentrations. Furthermore, in all the studies reporting a beneficial effect of cholecalciferol supplementation on inflammatory markers or disease activity scores, higher cumulative doses were used (20, 25), in comparison to trials that did not meet these endpoints (22). As mentioned above, only one study using high cumulative cholecalciferol doses failed to demonstrate the benefit of vitamin D supplementation on the disease activity (24); nonetheless, the minimal increase of the vitamin D plasma concentration from baseline is a hint for low compliance of patients to the prescribed regimen.

Taken together, these findings suggest that RA patients could take advantage from vitamin D supplementation, both in terms of pain relief (when hypovitaminosis D is corrected) and immune system regulation (when higher 25(OH)vitamin D plasma concentrations are obtained using high-doses regimens). The problematic translation of the experimental findings to human

disease can be explained by the inadequacy of an *in vitro* system to faithfully replicate the complexity of vitamin D metabolism *in vivo*. Indeed, this is not only influenced by the systemic level of cholecalciferol activation but also by the activity of the inhibiting enzyme CYP24A1, whose role might be more relevant than predicted in the past.

Another crucial step occurring *in vivo* is the local activation of vitamin D, probably more common in the presence of sufficiently high levels of cholecalciferol. Macrophages (36) and DCs (37) express CYP27B1, the activating enzyme of the intermediate metabolite 25(OH) vitamin D, which directly activates 25(OH) vitamin D in significant amount *ex vivo* (38).

25(OH) vitamin D concentration in the synovial fluid is approximately double the plasmatic level (39), and its anti-inflammatory effect is seen at about 50-100 nM in the presence of activating cells like APCs. Thus, the plasma concentration required for ensuring bone health is very likely too low to enhance any immunomodulatory effects (40). Therefore, only by using high doses of cholecalciferol, which seem well tolerated and safe, levels of vitamin D sufficiently high to enable its immunosuppressive effect locally on synovial tissue could be reached (41).

Finally, the response to vitamin D *in vivo* may also be influenced by VDR polymorphisms. Since the TaqI and FokI polymorphisms have been previously associated with RA susceptibility (42), it is plausible that they might also play a role in regulating the individual response to cholecalciferol supplementation.

Concerning the efficacy of different compounds, only one study has so far investigated the use of ergocalciferol, concluding that this is not advisable based on its ineffectiveness (23). On the contrary, alfacalcidol looks a promising agent; being an already active form of vitamin D, however, it may be burdened by a higher risk of hypercalcaemia and hypercalciuria than cholecalciferol, which should probably be considered the first-line agent in subjects with normal renal function (27).

Regarding RA flares, despite none of

the two studies assessing vitamin D efficacy revealed a significant beneficial effect, a recent meta-analysis suggests a potential role for vitamin D in this context. In fact, while no individual study met the endpoint, the cumulative analysis of the two study populations was close to significant. Further studies are required to elucidate this specific issue better (43).

Finally, it should be pointed out that the ability of vitamin D to suppress secondary hyperparathyroidism might be partially compromised in patients affected by autoimmune diseases (44), and this fact may contribute to the development of RA-related osteoporosis. Since hypovitaminosis D is highly prevalent in autoimmune conditions (45-48), the correction of hypovitaminosis D is paramount in the management of RA, even if the best regimen to be used is still debated (49-51).

We have to acknowledge some limitations: first of all, our systematic review is focused on a topic which has recently been explored by a meta-analysis (43), including 5/11 of the papers considered in the present paper. However, the findings of the two papers are consistent.

Moreover, the limitations underpinned when discussing the studies selected obviously affect the reliability of our findings. Patient population, outcome definitions and vitamin D schemes change across different studies, making them difficult to be compared. Finally, the largest part of evidences belongs to studies with small sample size, which might have affected the power of the findings.

In conclusion, a potential role for cholecalciferol in the management of RA can be hypothesised, although the doses required to evoke the immunomodulatory effects of vitamin D might be significantly higher than those currently used for hypovitaminosis correction. Despite the available evidence is not strong enough to support the use of cholecalciferol as a DMARD in RA and further studies are required to elucidate this aspect better, the achievement of an adequate vitamin D status in this context is likely beneficial and should be given primary importance in the management of RA patients.

References

1. CHRISTAKOS S, LIEBEN L, MASUYAMA R, CARMELIET G: Vitamin D endocrine system and the intestine. *Bonekey Rep* 2014; 3: 496.
2. JEON US: Kidney and calcium homeostasis. *Electrolyte Blood Press* 2008; 6: 68-76.
3. KIM S, YAMAZAKI M, ZELLA LA et al.: Multiple enhancer regions located at significant distances upstream of the transcriptional start site mediate RANKL gene expression in response to 1,25-dihydroxyvitamin D3. *J Steroid Biochem Mol Biol* 2007; 103: 430-34.
4. WALTERS MR: Newly identified actions of the vitamin D endocrine system. *Endocr Rev* 1992; 13: 719-64.
5. BIKLE DD: Vitamin D and the immune system: role in protection against bacterial infection. *Curr Opin Nephrol Hypertens* 2008; 179: 348-52.
6. ZHANG Y, LEUNG DY, RICHERS BN et al.: Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. *J Immunol* 2012; 188: 2127-35.
7. GRIFFIN MD, LUTZ WH, PHAN VA, BACHMAN LA, MCKEAN DJ, KUMAR R: Potent inhibition of dendritic cell differentiation and maturation by vitamin D analogs. *Biochem Biophys Res Commun* 2000; 270: 701-8.
8. GAUZZI MC, PURIFICATO C, DONATO K et al.: Suppressive effect of 1alpha,25-dihydroxyvitamin D3 on type I IFN-mediated monocyte differentiation into dendritic cells: impairment of functional activities and chemotaxis. *J Immunol* 2005; 174: 270-6.
9. CHEN S, SIMS GP, CHEN XX, GU YY, CHEN S, LIPSKY PE: Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *J Immunol* 2007; 179: 1634-47.
10. CIPPITELLI M, FIONDA C, DI BONA D et al.: Negative regulation of CD95 ligand gene expression by vitamin D3 in T lymphocytes. *J Immunol* 2002; 168: 1154-66.
11. RIGBY WF, DENOME S, FANGER MW: Regulation of lymphokine production and human T lymphocyte activation by 1,25-dihydroxyvitamin D3. Specific inhibition at the level of messenger RNA. *J Clin Invest* 1987; 79:1659-64.
12. CANTORNA MT, WOODWARD WD, HAYES CE, DELUCA HF: 1,25-dihydroxyvitamin D3 is a positive regulator for the two anti-encephalitogenic cytokines TGF-beta 1 and IL-4. *J Immunol* 1998; 160: 5314-9.
13. SLOKA S, SILVA C, WANG J, YONG VW: Predominance of Th2 polarization by vitamin D through a STAT6-dependent mechanism. *J Neuroinflammation* 2011; 8: 56.
14. HUHTAKANGAS JA, VEIJOLA J, TURUNEN S et al.: 1,25(OH)2D3 and calcipotriol, its hypocalcemic analog, exert a long-lasting anti-inflammatory and anti-proliferative effect in synoviocytes cultured from patients with rheumatoid arthritis and osteoarthritis. *J Steroid Biochem Mol Biol* 2017; 173: 13-22.
15. FAN P, HE L, HU N et al.: Effect of 1,25-(OH)2D3 on proliferation of fibroblast-like synoviocytes and expressions of pro-inflammatory cytokines through regulating microRNA-22 in rat model of rheumatoid arthritis. *Cell Physiol Biochem* 2017; 42: 145-55.
16. TETLOW LC, WOOLLEY DE: The effects of 1 alpha,25-dihydroxyvitamin D(3) on matrix metalloproteinase and prostaglandin E(2) production by cells of the rheumatoid lesion. *Arthritis Res* 1999; 1: 63-70.
17. BELLAN M, PIRISI M, SAINAGHI PP: Osteoporosis in rheumatoid arthritis: role of the vitamin D/parathyroid hormone system. *Rev Bras Reumatol* 2015; 55: 256-63.
18. BELLAN M, SAINAGHI PP, PIRISI M: Role of vitamin D in rheumatoid arthritis. *Adv Exp Med Biol* 2017; 996: 155-68.
19. DREYER, I, REED CI: The treatment of arthritis with massive doses of vitamin D. *Arch Phys Ther* 1935; 16: 537.
20. BROHULT J, JONSON B: Effects of large doses of calciferol on patients with rheumatoid arthritis. A double-blind clinical trial. *Scand J Rheumatol* 1973; 2: 173-6.
21. GOPINATH K, DANDA D: Supplementation of 1,25 dihydroxy vitamin D3 in patients with treatment naive early rheumatoid arthritis: a randomised controlled trial. *Int J Rheum Dis* 2011; 14: 332-9.
22. BUONDONNO I, ROVERA G, SASSI F et al.: Vitamin D and immunomodulation in early rheumatoid arthritis: A randomized double-blind placebo-controlled study. *PLoS One* 2017; 12: e0178463.
23. HANSEN KE, BARTELS CM, GANGNON RE, JONES AN, GOGINENI J: An evaluation of high-dose vitamin D for rheumatoid arthritis. *J Clin Rheumatol* 2014; 20: 112-4.
24. SALESI M, FARAJZADEGAN Z: Efficacy of vitamin D in patients with active rheumatoid arthritis receiving methotrexate therapy. *Rheumatol Int* 2012; 32: 2129-33.
25. CHANDRASHEKARA S, PATTED A: Role of vitamin D supplementation in improving disease activity in rheumatoid arthritis: an exploratory study. *Int J Rheum Dis* 2017; 20: 825-31.
26. ADAMI G, ROSSINI M, BOGLIOLO L et al.; STUDY GROUP ON OSTEOPOROSIS AND METABOLIC SKELETAL DISEASES OF THE ITALIAN SOCIETY OF RHEUMATOLOGY (SIR): An exploratory study on the role of vitamin D supplementation in improving pain and disease activity in rheumatoid arthritis. *Mod Rheumatol* 2018 Oct 4 [Epub ahead of print].
27. ANDJELKOVIC Z, VOJINOVIC J, PEJNOVIC N et al.: Disease modifying and immunomodulatory effects of high dose 1 alpha (OH) D3 in rheumatoid arthritis patients. *Clin Exp Rheumatol* 1999; 17: 453-6.
28. SOUBRIER M, LAMBERT C, COMBE B et al.: A randomised, double-blind, placebo-controlled study assessing the efficacy of high doses of vitamin D on functional disability in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2018; 36: 1056-60
29. YANG J, LIU L, ZHANG Q, LI M, WANG J: Effect of vitamin D on the recurrence rate of rheumatoid arthritis. *Exp Ther Med* 2015; 10: 1812-16.
30. DEHGHAN A, RAHIMPOUR S, SOLEYMANI-SALEHABADI H, OWLIA MB: Role of vitamin D in flare ups of rheumatoid arthritis. *Z Rheumatol* 2014; 73: 461-4.
31. MCWILLIAMS DF, WALSH DA: Pain mechanisms in rheumatoid arthritis. *Clin Exp Rheumatol* 2017; 35: 94-101.
32. ROCHE PA, KLESTOVAC A, HEIM HM: Description of stable pain in rheumatoid arthritis: a 6 year study. *J Rheumatol* 2003; 30: 1733-38.
33. YESIL H, SUNGUR U, AKDENIZ S et al.: Association between serum vitamin D levels and neuropathic pain in rheumatoid arthritis patients: A cross-sectional study. *Int J Rheum Dis* 2018; 21: 431-39.
34. LEE P, CHEN R: Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. *Arch Intern Med* 2008; 168: 771-72.
35. BASIT A, BASIT KA, FAWWAD A et al.: Vitamin D for the treatment of painful diabetic neuropathy. *BMJ Open Diabetes Res Care* 2016; 4: e000148
36. MONKAWA T, YOSHIDA T, HAYASHI M, SARUTA T: Identification of 25-hydroxyvitamin D3 1alpha-hydroxylase gene expression in macrophages. *Kidney Int* 2000; 58: 559-68.
37. FRITSCHKE J, MONDAL K, EHRNSPERGER A, ANDREESSEN R, KREUTZ M: Regulation of 25-hydroxyvitamin D3-1 alpha-hydroxylase and production of 1 alpha,25-dihydroxyvitamin D3 by human dendritic cells. *Blood* 2003; 102: 3314-6.
38. SMITH SJ, HAYES ME, SELBY PL, MAWER EB: Autocrine control of vitamin D metabolism in synovial cells from arthritic patients. *Ann Rheum Dis* 1999; 58: 372-8.
39. FAIRNEY A, STRAFFEN AM, MAY C, SEIFERT MH: Vitamin D metabolites in synovial fluid. *Ann Rheum Dis* 1987; 46: 370-4.
40. JEFFERY LE, WOOD AM, QURESHI OS et al.: Availability of 25-hydroxyvitamin D(3) to APCs controls the balance between regulatory and inflammatory T cell responses. *J Immunol* 2012; 189: 5155-64.
41. MCCULLOUGH P, AMEND J: Results of daily oral dosing with up to 60,000 international units (iu) of vitamin D3 for 2 to 6 years in 3 adult males. *J Steroid Biochem Mol Biol* 2017; 173: 308-12.
42. TIZAOUI K, HAMZAOUI K: Association between VDR polymorphisms and rheumatoid arthritis disease: Systematic review and updated meta-analysis of case-control studies. *Immunobiology* 2015; 220: 807-16.
43. FRANCO AS, FREITAS TQ, BERNARDO WM, PEREIRA RMR: Vitamin D supplementation and disease activity in patients with immune-mediated rheumatic diseases: A systematic review and meta-analysis. *Medicine* (Baltimore). 2017; 96: e7024.
44. SAINAGHI PP, BELLAN M, ANTONINI G, BELLOMO G, PIRISI M: Unsuppressed parathyroid hormone in patients with autoimmune/inflammatory rheumatic diseases: implications for vitamin D supplementation. *Rheumatology* (Oxford) 2011; 50: 2290-6.
45. ROSSINI M, MADDALI BONGI S, LA MONTAGNA G et al.: Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants and associations with disease activity and disability. *Arthritis Res Ther* 2010; 12: R216.
46. VOJINOVIC J, TINCANI A, SULLI A et al.: European multicentre pilot survey to assess vitamin D status in rheumatoid arthritis patients and early development of a new Patient

- Reported Outcome questionnaire (D-PRO). *Autoimmun Rev* 2017; 16: 548-54.
47. SAINAGHI PP, BELLAN M, CARDA S *et al.*: Hypovitaminosis D and response to cholecalciferol supplementation in patients with autoimmune and non-autoimmune rheumatic diseases. *Rheumatol Int* 2012; 32: 3365-72.
48. DALL'ARA F, CUTOLO M, ANDREOLI L, TINCANIA, PAOLINO S: Vitamin D and systemic lupus erythematosus: a review of immunological and clinical aspects. *Clin Exp Rheumatol* 2018; 36: 153-62.
49. SAINAGHI PP, BELLAN M, NERVIANI A *et al.*: Superiority of a high loading dose of cholecalciferol to correct hypovitaminosis d in patients with inflammatory/autoimmune rheumatic diseases. *J Rheumatol* 2013; 40: 166-72.
50. KUWABARA A, TSUGAWA N, TANAKA K *et al.*: Improvement of vitamin D status in Japanese institutionalized elderly by supplementation with 800 IU of vitamin D(3). *J Nutr Sci Vitaminol* 2009; 55: 453-8.
51. VON RESTORFF C, BISCHOFF-FERRARI HA, THEILER R: High-dose oral vitamin D3 supplementation in rheumatology patients with severe vitamin D3 deficiency. *Bone* 2009; 45: 747-9.