

# A randomised, double-blind, placebo-controlled study assessing the efficacy of high doses of vitamin D on functional disability in patients with rheumatoid arthritis

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## Abstract

### Objective

To evaluate the short-term efficacy of vitamin D (cholecalciferol) supplementation on functional disability in RA patients.

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### Methods

1. Patients: RA (ACR 1987 revised criteria) in non-remission (DAS28 >2.6) whose treatment was not expected to be changed over a 3-month period following inclusion and presenting with vitD deficits (serum 25OHD <30ng/mL). 2. Study design: prospective randomised placebo-controlled trial (NCT02243800). 3. Study arms: either vitD ampoules (cholecalciferol 100,000IU) or placebo. 4. Outcome measures: primary: improvement in patients' functional disability using the Health Assessment questionnaire (HAQ); secondary: improvement in DAS28ESR, DAS28CRP, ESR, CRP, RAID score, fatigue (EVA and FACIT), and SF36.

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### Results

Overall, 59 patients were included, 83.1% females, aged 59.8±10.9 years on average, with RA for 17.0±9.7 years. Thirty patients received placebo and 29 vitD. At 6 months, HAQ scores tended to be increased in the placebo group (+0.08±0.25), while slightly numerically decreased in the vitD group (-0.03±0.23) (p=0.11). After adjusting for age, gender, season, and initial vitD status, the between-group difference achieved statistical significance (p=0.046). After adjusting for age, gender, season, and initial vitD status, there was no significant difference in the secondary criteria between the 2 groups except for ESR and CRP (p=0.002 and 0.04, respectively).

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### Conclusion

In this randomised, double-blind, placebo-controlled clinical trial in patients with RA and VitD deficiency, high doses of cholecalciferol resulted in a statistically significant improvement in functional disability at month 6, which, however, was clinically not relevant.

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### Key words

vitamin D, cholecalciferol, vitamin D supplementation, rheumatoid arthritis

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## Introduction

The vitamin D (vitD) effects on bone have been well-documented, with 1,25(OH)<sub>2</sub>vitD<sub>3</sub> or calcitriol, the biologically active form of vitD, shown to facilitate the intestinal absorption of calcium (1). Calcitriol exerts its effects by binding to the vitD receptor (VDR), a nuclear receptor acting as a transcription factor. The discovery of VDR expression in almost all human cells has further focused the attention of the scientific community towards the extraskeletal effects of vitD (1). In this setting, prospective studies conducted so far reported moderate to strong inverse associations between 25-hydroxyvitamin D (25[OH]D) usually used as a proxy for individual's vitamin D concentrations and cardiovascular diseases, serum lipid concentrations, serum inflammation markers, glucose metabolism disorders, weight gain, infectious diseases, mood disorders, declining cognitive function, as well as impaired physical functioning (2). By contrast, intervention studies on vitD supplementation revealed little to no impact on these disorders (2).

The immunomodulatory role of VitD has also been put forth, on account of VDRs being present on immunitary cells, with numerous mechanisms of action on immune cells presently under discussion (1). For these reasons, a number of vitD research studies have been conducted in clinical conditions like multiple sclerosis, Crohn's disease, and systemic lupus erythematosus (1). Despite the inverse correlation between 25[OH]D levels and disease activity revealed by most studies, the clinical usefulness of vitD supplementation for managing these conditions is still a matter of debate (1).

VitD was shown to be involved in collagen-induced arthritis, while hypothetically modulating the Th17 pathway (3). In murine rheumatoid arthritis (RA) models, disease symptoms were prevented by dietary vitD supplementation (4). In humans, RA incidence was demonstrated to be inversely correlated to serum vitD levels (5). In the meta-analysis carried out by Song *et al.*, patients with the highest total vitD intake displayed a 24.2%-decreased relative

risk (RR) (RR=0.758, 95% CI=0.577-0.937) to develop RA, as compared to those with the lowest total vitD intake (5). The meta-analysis conducted by Lin *et al.* involving 2,148 patients and 1,991 controls revealed RA patients to exhibit lower 25[OH]D levels than controls (6). Interestingly, an inverse correlation between 25[OH]D levels and RA activity was found in this study, in accordance with the report published shortly thereafter by our research team (7). These observations do not necessarily imply vitD's immunomodulatory activity in the RA setting, given that low 25[OH]D levels could either be the cause or consequence of increased RA activity. In order to ascertain the immunomodulatory activity exerted by vitD, further clinical studies must be performed. Seven previous clinical trials three with 1(OH)vitD<sub>3</sub>, one with 1,25dihydroxyvitamin D<sub>3</sub>, one with 25(OH)D, one with ergocalciferol and one with colecalciferol were conducted, though with poor design methodology and contradictory data (8-16).

For these reasons, we implemented a double-blind randomised placebo-controlled 24-week study, primarily designed to investigate whether vitD supplementation was able to improve the functional handicap in RA patients, in non-remission (DAS28 >2.6), suffering from vitD deficiency (serum 25[OH]D <30ng/mL).

## Materials and methods

### *Study design and participants*

To be eligible for study entry, patients had to be older than 18 years, suffer from RA according to the revised 1987 ACR criteria, be in non-remission (DAS28 >2.6), display serum 25[OH]D levels <30 ng/mL, and with no treatment modification envisaged by the investigator in the near future. In addition, no change in disease-modifying RA treatment was allowed to have occurred within the last 3 months prior to baseline, with patients not permitted to have undergone intra-articular infiltrations over the last 2 months. Corticosteroid intake was authorised only if the administered daily dose was stable and <10 mg prednisone equivalent. The non-inclusion criteria were as follows:

ACR functional Class IV, hypercalcaemia exceeding  $>2.6\text{mmol/L}$ , known hypercalciuria exceeding  $4\text{mg/kg/day}$ , history of kidney stone colic, thiazide intake, as well as pregnancy or lactation. The study was carried out in accordance with the principles of the Declaration of Helsinki, and the protocol was approved by the ethics committee (IRB number: AU869) of the South-East region and registered on ClinicalTrials.org (NCT02243800). Patients provided written informed consent prior to enrollment and before any study-related procedures were undertaken.

#### Randomisation and blinding

Patients were randomised according to a 1:1 ratio to receive either vitD (100,000IU vial) or placebo. Initial vitD dosage was based on baseline serum 25[OH]D levels. Patients exhibiting 25[OH]D  $<10\text{ ng/mL}$  were given 2 vials every 2 weeks for 2 months; those with 25[OH]D levels between 10 and 20 ng/mL received 2 vials every 2 weeks for 1.5 months; those with 25[OH]D levels between 20 and 30 ng/mL received 2 vials every 2 weeks for 1 month. After administering the loading dose, all patients were given 1 vial every 4 weeks until the 24th week. Patients were assessed at Week 24.

#### Primary outcome parameters

The study was primarily aimed to demonstrate that vitD therapy was able to improve RA patients' functional handicap as based on the Health assessment questionnaire (HAQ). Considering the efficacy of anti-rheumatic treatments currently available for managing RA, we deemed it unethical to assess vitD efficacy using the disease activity criteria. This would have needed the inclusion of RA patients with at least moderate disease activity.

#### Secondary outcome parameters

The study's secondary objectives were to investigate whether vitD therapy resulted in diminished RA activity, as based on DAS28-ESR, DAS28-CRP, total number of tender joints, total number of swollen joints, visual analogue scale (VAS) for pain, VAS for activity, erythrocyte sedimentation rate (ESR),

and C-reactive protein (CRP), EULAR response, decrease in asthenia (VAS and FACIT-fatigue), and improvement in RA impact of disease (RAID) score. The impact of vitD supplementation on quality of life was assessed using the 36-Item Short Form Health Survey (SF-36).

#### Statistical analyses

Considering a standard deviation of 0.45 we calculated that a sample of 74 patients in each group would provide 90% power to detect a difference in HAQ (primary outcome) of at least 0.24 between baseline and 6 months, for a two-sided type-I error at 0.05. Finally, 82 patients should be included per group, *i.e.* 164 patients for the whole protocol, to take into account lost to follow-up. Statistical analyses were carried out using Stata software (Version 13, StataCorp, College Station, TX, US). All tests were two-sided with a Type I error set at 0.05, with all analyses conducted on the intention-to-treat population. Continuous data were expressed as mean  $\pm$  standard deviation (SD) or median with interquartile range [IQR] depending on statistical distribution, and categorical parameters as frequencies and associated percentages. Between-group (placebo *vs.* vitD supplementation) comparisons of continuous data, such as primary endpoints, were conducted using the Student's *t*-test, or Mann-Whitney test when *t*-test assumptions were not met. Normality was investigated by means of the Shapiro-Wilk test, and homoscedasticity by the Fisher-Snedecor test. Linear mixed models were then employed to take into account within- and between-centre variability. The residual normality of these models was investigated as described previously. When appropriate, logarithmic transformation was proposed to achieve normality. Concerning categorical data, Chi-squared or Fisher's exact tests were performed prior to applying generalised linear mixed models (logistic regression). Multivariate analyses were carried out taking into account possible confounding parameters determined according to univariate analysis results and clinical relevance, such as age, gender, season

of study enrolment, and baseline vitD levels. All comparisons at 6 months were conducted considering baseline value as covariate (as an ANCOVA, according to Vickers and Altman).

## Results

### Patients at baseline

Overall, 59 RA patients were enrolled in the study, 30 of whom were assigned to placebo group and 29 to vitD group, with baseline demographics and patient characteristics listed in Table I.

Of the patients enrolled, 83.1% were female, aged  $59.8\pm 10.9$  years on average, and suffering from RA for  $17.0\pm 9.7$  years. In this patient population, 13 patients exhibited serum 25[OH]D levels  $<10\text{ng/mL}$ , twenty-three 25[OH]D levels between 10 and 20ng/mL, and twenty-three 25[OH]D levels between 20 and 30ng/mL. Overall, 69.5% tested positive for rheumatoid factor, and 64.4% for anti-cyclic citrullinated peptide (anti-CCP). Body mass index (BMI) was  $26.4\pm 5.2$ , with 13.6% of patients being smokers. Among the patients, 35.6% were treated with corticoids, 43 (72.9%) with methotrexate (MTX), and 49 (83.1%) using biotherapy (anti-TNF [n=18], tocilizumab [n=15], abatacept [n=14], and rituximab [n=2]).

At baseline, the Health assessment questionnaire (HAQ) score was  $1.05\pm 0.74$ , DAS-ESR  $3.7\pm 0.8$ , and DAS-CRP  $3.5\pm 0.8$ . The RA impact of the disease (RAID) was estimated at 4.1 (range: 3.0–5.4), FACIT fatigue at 34 (range: 26–44), SF36 physical component score at  $37.9\pm 8.6$ , and SF-36 mental component score at  $46.5\pm 10.2$ .

### 6-month primary outcome data

At 6 months, when no adjustments were made, there was no significant difference between the vitD and placebo groups as regards with the primary efficacy parameter, namely the HAQ score. The HAQ score tended to increase in the placebo group ( $+0.08\pm 0.25$ ), while slightly diminishing in the vitD group ( $-0.03\pm 0.23$ ) ( $p=0.11$ ). After adjusting for age, gender, season, and initial vitD status, the between-group difference achieved statistical significance (Vit D group  $-0.03\pm 0.23$  *vs.*  $0.08\pm 0.25$  placebo group,  $p=0.046$ ).

In the subgroup of patients exhibiting serum 25[OH]D levels <20ng/mL, there was a significant decrease in HAQ score observed at 6 months in patients given vitD (-0.12 [-0.19, +0.19]), as compared to those receiving placebo (+0.12 [-0.06, 0.25]) ( $p=0.03$ ).

#### Six-month secondary outcome measures

After adjusting for age, gender, season, and initial vitD status, a significant improvement in inflammatory syndrome, namely ESR and CRP levels, was noted in the vitD group as compared to placebo groups, with  $p$ -values of 0.002 and 0.04, respectively.

Additionally, in the group given vitD, there was a trend towards a superior improvement in DAS28-ESR observed in the vitD group, in comparison with placebo. However, the between-group differences did not reach statistical significance. A good-to-moderate EULAR response was not more frequently encountered with vitD than placebo.

#### Six-month quality of life

There was no difference in patients' global assessments, VAS pain, VAS activity, VAS fatigue, or RAID observed between both groups, nor did patients' quality of life (SF-36) concerning physical or mental component scores display any differences.

#### Discussion

Based on the VDR expression in synovial cells of RA patients, in addition to vitD's immunomodulatory activity observed *in vitro* and in murine RA, we elaborated the hypothesis that supplementation with vitD to achieve normal levels would positively impact RA management. In our view, treatment with vitD had thus the potential to figure as adjuvant therapy able to diminish RA patients' functional handicap.

Unlike our expectations at trial initiation, study data analyses revealed only a slight improvement in HAQ observed in vitD-treated patients, with a slight deterioration in those receiving placebo. To us, this result, though statistically significant, did not appear to be clinically relevant. Besides, the small HAQ amelioration observed may be equally

accounted for by vitD's effects on muscle function than by its immunomodulatory activity. Besides, as compared to placebo, an improvement in inflammatory syndrome markers (ESR and CRP) occurred in patients given vitD supplementation versus placebo, with no between-group differences observed on the other secondary outcome parameters, such as DAS 28, fatigue, RAID, or SF-36 scores kept unaffected.

In humans, five previous clinical trials were performed with 1(OH)vitD<sub>3</sub>, resulting in contradictory results. In the study by Andjelkovic *et al.*, 19 RA patients were administered alfacalcidol at a daily dose of 2µg. After a 3-month treatment, nine (45%) patients were in remission and eight (44%) exhibited beneficial treatment effects (8). In the study by Yamauchi *et al.*, 140 patients were given daily doses of either placebo or alfacalcidol at 1 or 2µg during 16 weeks. As a result, only 10% of alfacalcidol patients displayed RA activity (9). In the open study by Hein *et al.*, 20 patients were given 1µg alfacalcidol over 8 weeks, with no significant decrease in the number of tender or swollen joints or improvement in inflammation parameters (ESR, CRP) observed (10). Lastly, in a study by Yang *et al.*, 377 patients were classed in two groups, one with normal vitD levels ( $n=168$ ), and the other with vitD deficiency (11). Of the latter, 84 patients were given alfacalcidol at a dose of 0.25µg twice daily, the remaining patients figuring as control group ( $N=88$ ). The reported rates of RA recurrence were 16.7% in the normal-vitD group, 19% in the vitD-deficient group that also received alfacalcidol, and 29.5% in the vitD-deficient group that remained untreated. As a result, the RA recurrences rates were statistically lower in the normal-vitD compared to the vitD-deficient group, though the differences between treated and non-treated patients did not reach statistical significance. In the open study by Gopinath *et al.*, 110 patients upon triple treatment initiation consisting of methotrexate, salazopyrin, and hydroxychloroquine were randomised to receive either 1, 25 dihydroxy vitD<sub>3</sub> supplementation (500IU x per day) or calcium alone over a 3-month period (12). An

improvement in VAS pain corresponding to a 50mm change was noted in the vitD ( $n=59$ ) group and to a 30mm change in the calcium-alone group ( $n=62$ ), the between-group difference being statistically significant ( $p=0.006$ ) (12). In the study by Salesi *et al.*, 117 patients with active RA despite stable MTX for 24 weeks were randomized to receive either placebo or 50 000IU 25(OH)D per week over 12 weeks (13). In these patients, mean vitD levels proved to be in the normal range. At 12 weeks, no statistically significant differences in either DAS or DAS-related parameters were shown between both groups (13). A randomised placebo-controlled study was carried out with vitD<sub>2</sub> (14). In this study, a small group of patients ( $n=22$ ) was randomized to receive either placebo or 50 000IU vitD<sub>2</sub> vials three times per week during the first 4 weeks, and then two times per month during the next 11 months. Whereas no significant improvement in either DAS-28 or HAQ was observed, there was an aggravation in pain and deterioration on global assessment in vitD<sub>2</sub>-treated patients. Owing to the study's small sample size, no firm conclusions can be drawn from these data (14). In the Dehgan *et al.* study, 80 RA patients on remission and with vitD deficiency (vitD <30ng/dL) were given either placebo or 50,000IU vitD (cholecalciferol) per week over 24 weeks. Neither was there a decrease in the risk of recurrence or a significant improvement in DAS observed (15).

Lately, Franco *et al.* performed a meta-analysis based on four RA studies (17). In two of these studies, no improvement in RA activity was shown (VAS or DAS) (13, 14), whereas in the two others, there was a reduction in RA recurrence risk, which, nonetheless, was statistically non-significant (11, 15).

Lastly, a recent open-label study assessed the efficacy of vitD supplementation, given at a dose 60 000 IU/week for 6 weeks, then every month for 3 months, in RA patients in non-remission (DAS-CRP>2.6) with vitD <20ng/mL (16). In 59 evaluated patients, a significant improvement in DAS28-CRP was observed (DAS28; CRP: 3.08±1.11 vs. 3.68±0.93), as well as a significant reduction in the number of swollen and

painful joints, yet without any improvement in inflammatory parameters (ESR and CRP).

So far, there are still numerous unresolved issues concerning vitD's immunomodulatory activities in the RA indication. First, there has been no firm consensus yet as to the recommended serum levels to target, nor has there been any agreement regarding the optimal mode of vitD administration. It must also be highlighted here that there are several open questions as to whether different forms of VitD, such as vitD2, vitD3, or vitD analogs, exhibit specific advantages concerning their immunomodulatory responses (18).

**Study limitations.** Our study, however, exhibits several limitations that must be highlighted herein, preventing us to conclude that administering vitD to RA patients induces key benefits or none. The trial's major limitation is its small sample size, consisting of only 59 patients, which can be explained by the difficulties encountered with patient enrollment. At study start, there was a lot of keenness for vitD supplementation, and recruiting patients who were not yet on vitD supplementation proved quite challenging. Another study drawback was that we are still unsure whether satisfactory vitD levels were achieved at study end in our vitD-deficient patients. Though a central serum vitD level reading was initially scheduled as per study protocol at study end, such measurements were not conducted due to unresolved technical issues. Despite this, it can be assumed that satisfactory vitD levels were obtained, given that the doses applied in our study were markedly higher than those tested by Schleck *et al.*, which proved able to correct vitD deficiencies in all possible scenarios (19).

In conclusion, this randomised, double-blind, placebo-controlled trial involving vitD-deficient RA patients, high doses

of cholecalciferol were shown to result in a small, though significant, statistical improvement in functional disability after a 6-month treatment period, which was clinically not relevant. No amelioration was seen in RA activity parameters, except for those pertaining to the inflammatory syndrome. However, in our opinion, these findings should be considered as an argument in favor of vitD supplementation for RA patients exhibiting non-optimal vitD levels, in the aim to improve their handicap.

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