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Impact of vitamin D supplementation on disease activity and pain management in rheumatoid arthritis: a randomized double-blinded controlled study

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Abstract

Background Rheumatoid arthritis (RA) is a progressive autoimmune disease. During complex therapy, vitamin D supplementation could have an immunomodulatory effect and improve disease activity.

Aim The aim of this study was to investigate the effects of vitamin D supplementation on laboratory parameters and the disease course among patients with RA.

Methods This prospective, randomized, parallel-group, double-blind study with a follow-up period of 6 months aimed to investigate the effects of 4000 IU/day vitamin D on visual analogue scale (VAS) and disease activity score-28 (DAS-28) scores among RA patients treated at the Rheumatology Clinic of the University Clinical Centre of Kosova. The study included 100 RA patients (82 women and 18 men) who were divided into two groups: patients with vitamin D supplementation and patients without vitamin D supplementation.

Results Our results revealed no significant differences in baseline clinical or laboratory parameters between the study groups. At the beginning of the study, to ensure homogeneity between the study groups, we compared inflammatory mediators between groups. We found no significant differences in the IL6 (H statistic of 1.79 for p.180), IL17 (H statistic of 0.015 for p.902), TNF (H statistic of 1.15 for p.284), ESR (H statistic of 0.085 for p.771) or CRP (H statistic of 1.45 for p.229) levels between the two groups. After six months of supplementation therapy, the vitamin D group showed significant differences in pain reduction (VAS score, U'=2245.5; $P<0.0001$) and disease activity (DAS28 score, U'=2285.5; $P<0.0001$).

Conclusions Supplementation with 4000 IU/day of vitamin D can potentially improve disease activity and pain management among RA patients after six months. However, further research is needed with a focus on longer patient follow-up periods to determine the long-term benefits of vitamin D in RA patients.

Trial registration ID NCT06716476, Date of Registration 04.12.2024.

Keywords Rheumatoid arthritis, Vitamin D supplementation, VAS, DAS28

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Introduction

Rheumatoid arthritis (RA) is an idiopathic autoimmune disease that has a chronic course; and its exacerbations and remissions occur more frequently in women, and this disease is characterized by inflammation, pain and progressive damage to the joints [1]. RA is a disease of socio-epidemiological importance; it has a significant global burden, and its incidence and course are expected to increase due to population ageing, especially in developing countries. RA usually affects older adults. However, due to its increasing incidence, the average age of patients with first signs of RA is decreasing [2, 3].

Despite numerous advances in the optimization of RA therapy, this disease remains a major challenge for the health care system of many countries, and further research is needed to find therapeutic alternatives in order to improve treatment outcomes, increase patient adherence and prevent complete physical patient disability. The complex and multifaceted pathophysiology of RA suggests that modulation of the immune system may be a cornerstone of the treatment approach for this disease [4]. In this treatment strategy, the role of vitamin D is undeniable because of its influence on the immune system. However, while the role of vitamin D in influencing immune function and inflammation has been well documented, there are conflicting and inconclusive results concerning its effect on the progression of RA [5, 6].

The impairment of innate and adaptive immune function due to vitamin D deficiency has a triggering effect on the pathophysiological mechanism of RA. Vitamin D is recognized to have a role in the prevention of rheumatic diseases. However, there are inconsistencies in the literature regarding the therapeutic effects of vitamin D on RA disease progression and severity [7].

The progression of RA is monitored by measuring inflammatory mediators such as C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), tumour necrosis factor (TNF) and interleukin-6 (IL-6) [8]. There is evidence that vitamin D supplementation may reduce the burden of disease by controlling the release of different inflammatory mediators, and thus, vitamin D supplementation is considered beneficial for reducing disease activity [9].

The literature on the effects of vitamin D supplementation on DAS-28 scores and RAS progression yield encouraging findings compared to immunology results. In this context, high doses of vitamin D have been shown to have a positive effect on disease activity in patients with active RA disease and vitamin D deficiency [10].

While vitamin D could be one of several factors that impact the pathophysiological mechanism of RA, additional research is needed to clarify the immunomodulatory and anti-inflammatory effects of vitamin D as well as its role in the clinical amelioration of RA disease activity. More specifically, further research is needed to determine how supplementation with vitamin D influences disease modulation and pain levels in RA patients [11].

Even though Vitamin D is a fat-soluble hormone that has been the subject of extensive research, recent research has revealed that vitamin D plays a broad role in regulating immune system functions, which may also be involved in the development and progression of rheumatoid arthritis. Vitamin D and RA have a complicated interaction since vitamin D deficiency, which is common in RA patients, might raise the risk of osteoporosis, which is typical of RA [12]. The sensitivity of vitamin D levels to RA and RA activity in rheumatoid patients was conducted by Lee et al., who found a negative correlation between vitamin D levels and sensitivity to RA and RA activities; more specifically, the meta-analysis showed that vitamin D levels and RA activity were inversely related [13]. Despite the fact that higher vitamin D intake has been linked to a lower risk of developing other autoimmune illnesses, little is known about how it affects the risk and activity of RA [14]. Additionally, research on rheumatoid arthritis indicates that active vitamin D may be a useful parameter for controlling inflammation, that vitamin D may be a therapeutic biomarker, and that it may even be used to monitor the course of the disease and the effectiveness of treatment in rheumatoid arthritis patients [15].

This suggests that more studies are needed to demonstrate the clinical benefits of vitamin D supplementation in the treatment of RA. Thus, limited studies have assessed vitamin D as a supplement for the treatment of RA.

Therefore, this study aimed to investigate the effects of vitamin D on disease activity and progression among RA patients by comparing patients receiving vitamin D supplementation and patients not receiving vitamin D supplementation. Vitamin D potentially influences RA by regulating the immune system and supporting bone health. Vitamin D serum concentrations may influence the progression of RA disease over time, thus promoting beneficial treatment decisions.

The following research hypotheses have been derived from a review of the literature:

H1: Vitamin D supplementation significantly improves disease activity and inflammation levels in patients, as measured by reductions in DAS-28 scores and CRP levels compared to controls.

H2: Gender, age, and duration of diagnosis are significant predictors of change in DAS-28 and CRP levels.

Methodology

Trial design

This prospective, randomized controlled trial (RCT) involved a parallel group design, thus ensuring that disease activity was measured simultaneously and independently over time. Patients were allocated to group at a 1:1 ratio, thus ensuring that there was an equal number of participants in each group, thereby maintaining balance and enhancing the comparability of outcomes. No modifications were made to the study's design, procedures, or protocols following the commencement of the trial.

Ethics

Prior to recruitment, the research, including informed consent from patients, was approved by the Ethics Committee of the Faculty of Medicine, number 2598. Patients were only included in the study after they signed the informed consent form and were fully informed about the study. The research was conducted in accordance with the Declaration of Helsinki. The study was also registered in the clinical trial database with the ID NCT06716476, Date of Registration 04.12.2024.

Participants

The participants were Caucasian RA patients of Kosovar ethnicity and of both sexes who were aged 30–65 years and who met the diagnostic criteria for RA-ACR/EULAR 2010 [16].

The inclusion criteria were as follows: a proven diagnosis of RA-ACR/EULAR 2010, divided into four classifications with scores for each, i.e., joint symptoms, serology (including RF and/or ACPA), symptom duration (< 6 weeks or > 6 weeks), and acute phase reactants (CRP and/or ESR); scores of ≥ 6/10; and an RA disease duration of 1–14 years.

The exclusion criteria were as follows: other inflammatory diseases; thyroid and parathyroid diseases; liver and kidney diseases; treatment in the past 3 months with Ca > 1 g/per day; and treatment in the last 3 months with vitamin D supplements.

Study participants were recruited from a cohort of patients treated at the University Clinical Center of Kosova - Clinic of Rheumatology in Prishtina from 2022 to 2023.

Interventions

The primary intervention in this study was supplementation with vitamin D at a dosage of 4000 UI/day in the control group compared with the group of patients not receiving vitamin D supplementation. Vitamin D was administered in the form of capsules of vitamin D supplement (4000 IU vitamin D capsule manufactured by Erbozeta S.r.l., San Marino). Patients consumed the 4000 IU of vitamin D capsules once daily after breakfast. There was no change in medication among subjects during the follow-up period. The dose-response study on the efficacy and safety of taking vitamin D3 by Vieth et al. shows that vitamin D is safe and effective at a dosage of ≥ 100 μg/day = ≥ 4,000 IU/day [17].

Furthermore, the safety of this vitamin D dosage is discussed in a review article by Grant et al. As the cohort of study participants consisted of patients with rheumatoid arthritis, who generally require higher doses of vitamin D, we considered this to be an optimal dose for the purposes of this study [18].

We collected demographic data (age, sex, occupation), medical history, data on joint swelling and tenderness, visual analogue scale (VAS) scores for overall pain and DAS-28 scores. For the calculation of DAS-28 scores, C-reactive protein (CRP) was selected as the inflammatory marker, which is a critical factor in assessing disease activity and inflammation in patients with rheumatoid arthritis.

To ensure equality between the study groups prior to the intervention, we measured the concentrations of 25-hydroxyvitamin D 25(OH)D, CRP, anti-citrullinated peptide (ACPA) antibodies, IL-6 concentrations, IL-17 concentrations, TNF-alpha concentrations, and the erythrocyte sedimentation rate (ESR). The baseline values were as follows: 25-hydroxyvitamin D 25(OH)D, < 20 ng/mL; CRP, < 1.0 mg/dL; IL-6, < 12.0 pg/mL; IL-17, < 1.4 pg/ml; TNF-alpha, < 4.6 pg/ml; and ESR, 0–20 mm/h. The serum samples were collected in autumn, winter, and early spring.

Antirheumatic medication regimens were not adjusted in the enrolled patients during the study period due to ethical considerations, as treatment changes might compromise patient care.

Outcomes

The primary outcome was 25(OH)D levels at baseline in both groups of RA patients and the levels of RA inflammatory mediators (IL6, IL17, CRP, ESR, and TNF-alpha). The secondary outcomes of the study were disease activity at baseline and 6 months after supplementation with vitamin D, as indicated by DAS-28 scores and VAS scores.

Sample size

The total number of study participants was 100. This sample size ensured an effect size of 0.6 for the interpretation, a power of 80% and a significance level of 0.05.

$$n = \frac{2 \cdot (Z_\beta + Z_{\alpha/2})^2}{d^2}$$

Using the formula for a two-tailed t test, the required sample size for an effect size of 0.6, with 80% power and

a 5% significance level ($\alpha = 0.05$), was 44 patients with RA per group, thus yielding a total of 88 patients across the two groups. According to similar studies, to detect a clinically meaningful change in DAS28 (≥ 1.2), a sample size of 100 participants is considered adequate to capture a moderate to large effect [19].

Throughout the study, there were no missing data or participant dropouts, so neither per-protocol nor intention-to-treat analyses were applicable.

An interim analysis was not planned for this study, as it was designed to evaluate outcomes only after completing the full intervention period.

Randomization

To ensure a balanced distribution, we used the stratified randomization method. The sample was divided into subgroups based on age, sex and disease severity. Each participant had an equal chance of being randomly assigned to either a group of patients receiving vitamin D or a group without vitamin D. We used random even and odd numbers to assign study participants.

Allocation of study groups

After stratification, the 100 RA patients were randomly assigned by simple randomization into two groups on the basis of age, sex and disease severity.

The study group (vitamin D supplementation) included patients who received 4000 IU/day of vitamin D capsule. Before initiating the study, participants were informed about the potential adverse effects. During the study period, repeated blood analyses were conducted to monitor potential adverse events associated with the 4000 IU/day vitamin D dosage. No cases of hypercalcemia were detected, and none of the participants reported any symptoms of toxicity or adverse effects related to the treatment.

The control group included patients who did not receive 4000 IU/day of vitamin D capsule and were not given a placebo capsule; thus, no intervention was administered.

The participants were stratified into subgroups based on age, sex, and disease severity prior to randomization. The randomization sequence was generated manually. Allocation concealment was achieved through the use of sequentially numbered, opaque, sealed envelopes.

The sequence generation was performed by an independent statistician, whereas enrolment was carried out by an appointed research team member responsible for participant screening and informed consent. The assignment of participants to the respective study groups was conducted by an independent, blinded research assistant, who assigned participants to either the treatment or control group based on the concealed randomization sequence.

Methodology of blinding

To avoid study bias in the assessment of outcomes, we used the double-blind randomization method, in which neither the patient nor the researcher had any information about the group allocation or the intervention. The study nurse performed the enrolment and group allocation, while the clinical nurse administered vitamin D. Laboratory personnel and data analysts were blinded to group allocation.

Statistical methods

We used SPSS 25 and STATA software to analyse the data. For demographic data comparisons between the two groups of patients, the frequency distribution was analysed. The chi-square test was used to assess the associations between categorical variables, and Student's t test was used to compare the means of two different groups. For the clinical assessment of two groups, we conducted the Mann–Whitney U test to compare the distributions of two independent groups with ordinal data, whereas Fisher's exact test was used to assess associations in a 2×2 contingency table. We conducted ANOVA to measure and compare the effects of vitamin D on RA inflammatory mediator concentrations on four parameters (IL6, IL17, TNF and CRP).

We conducted multivariate linear regression analyses to examine the effect of vitamin D supplementation on clinical and inflammatory outcomes in patients with rheumatoid arthritis. Specifically, we assessed changes in DAS-28 scores and CRP levels from baseline to six months while adjusting for age, gender, baseline values, and duration of diagnosis.

Results

A total of 108 patients were assessed for eligibility to participate in the study. Of these, 104 patients met the eligibility criteria. At the end of the recruitment process, 50 patients were assigned to the vitamin D control group, and 50 patients were assigned to the group that did not receive vitamin D. Further details are provided in the CONSORT diagram in Fig. 1.

The study involved 100 patients with a confirmed diagnosis of RA, including 82 women and 18 men. In the group receiving vitamin D, a total of 43 patients (86.0%) were women, whereas in the control group, 39 (78.0%) were women. No significant difference was observed between the two study groups in terms of sex (Fisher test, $P = 0.435$, $P > 0.05$).

The mean age of the patients was 50.9 years (SD ± 5.7 years), with the most common age group (58.0%) being 50–59 years. In the vitamin D group, 74.0% of the patients were 50–59 years old, whereas in the control group, more than half of the patients were 40–49 years old. There was a significant difference in the mean age of

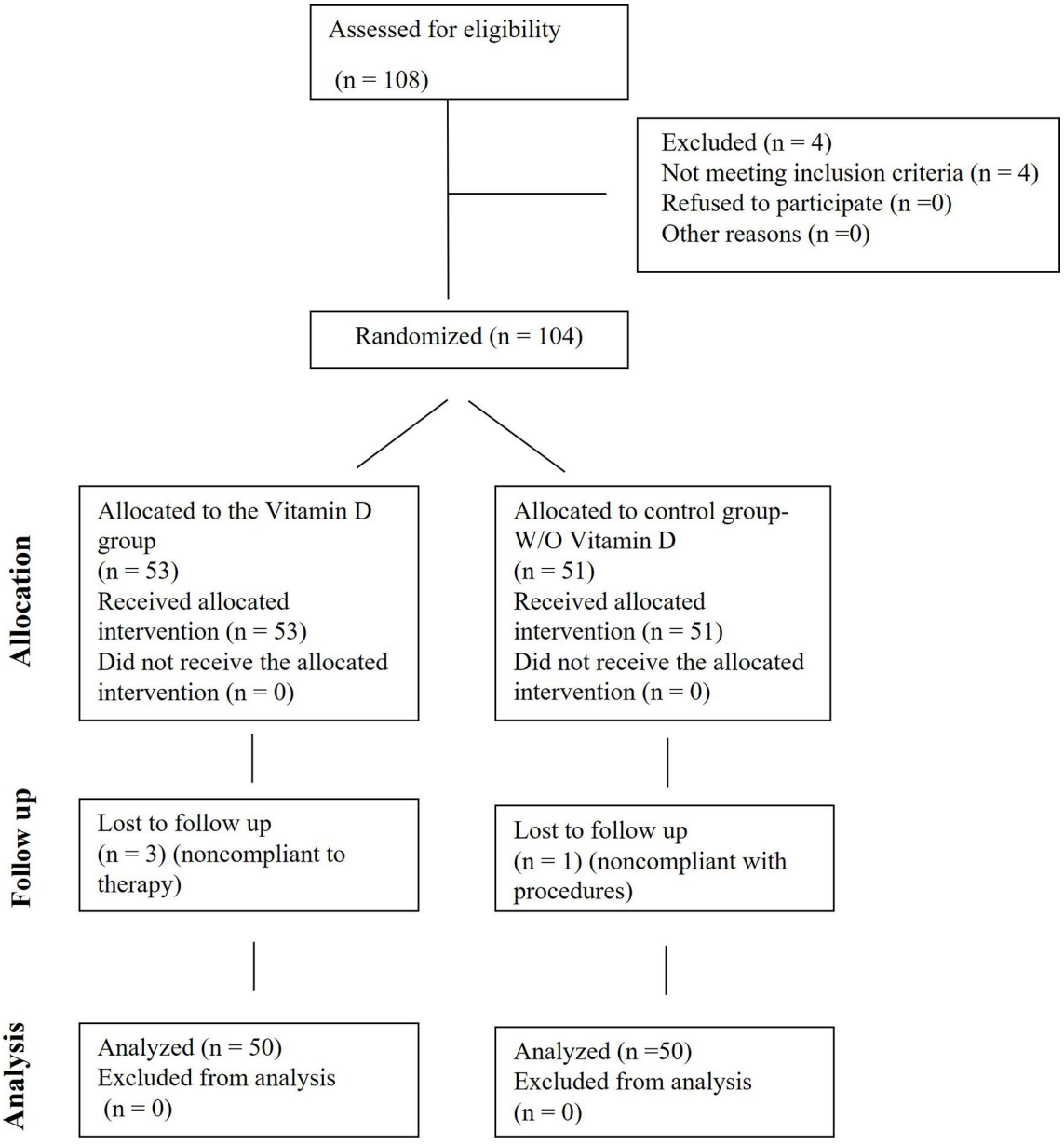

Fig. 1 CONSORT algorithm of study flow of participants through each stage of the randomized trial

patients between groups (U' = 1859.5, $P < 0.0001$). Among RA patients, housewife was the most common occupation, accounting for 45.0% of the patients (the group with vitamin D 48.0% vs. the control group 42.0%), followed by teachers (11.0%), economists (11.0%) and nurses (5.0%). Further demographic data are provided in Table 1.

In all the RA patients, changes were observed in 4 or more joints. In 95.0% of patients, changes were observed in more than 10 joints; in 5.0% of patients, changes were observed in 4 to 10 joints. There was no significant difference in the number of joint changes between the study groups ($P > 0.05$). Neuropathy, dry eyes and dry mouth were reported in 12.0% of the patients in both groups. A total of 8.0% of patients in both groups had carpal tunnel syndrome, and vasculitis and scleritis were less common extra-articular manifestations in both patient groups.

A positive rheumatoid factor (RF) or a high positive ACPA value was found in 77.0% of the RA patients (vitamin D group, 78.0% vs. control group, 76.0%), with no significant difference between the groups (Chi = 0.213, $P = 0.899$; i.e., $P > 0.05$). Males and females had serum 25(OH)D levels below the normal threshold of 20 ng/mL, indicating that vitamin D deficiency was prevalent across both sexes and study groups.

Further details describing the clinical characteristics of the RA patients in this study are provided in Table 2.

Table 1 Patient demographic data ($n=100$)

Gender	**Gr. W/Vit. D**		**Gr. WO/Vit. D**		**Total**		**Fisher test**
	N	**%**	***N***	**%**	***N***	**%**	
F	43	86.0	39	78.0	82	82.0	*P*=0.435
M	7	14.0	11	22.0	18	18.0	
Total	**50**	**100.0**	**50**	**100.0**	**100**	**100.0**	
Age-Group (Years)	**Gr. W/Vit. D**		**Gr. WO/Vit. D**		**Total**		
	N	**%**	**N**	**%**	**N**	**%**	**Chi-test P value**
30-39	1	2.0	1	2.0	2	2.0	Chi=17.2, *P*<0.0001
40-49	7	14.0	28	56.0	35	35.0	
50-59	37	74.0	21	42.0	58	58.0	
60+	5	10.0	-	-	5	5.0	
Total	**50**	**100.0**	**50**	**100.0**	**100**	**100.0**	
Age (Years)	**Gr. W/Vit. D**		**Gr. WO/Vit. D**		**Total**		**Mann–Whitney test**
N	50		50		100		U' = 1859.5, *P*<0.0001
Mean	53.2		48.7		50.9		
SD	5.5		5.0		5.7		
Min	36		32		32		
Max	62		58		62		
Occupation			**Gr. W/Vit. D**		**Gr. WO/Vit. D**		**Total**
			N	**%**	**N**	**%**	**N**	**%**
Administrator			3	6.0	6	12.0	9	9.0
Housewife			24	48.0	21	42.0	45	45.0
Nurse			4	8.0	1	2.0	5	5.0
Engineer			1	2.0	1	2.0	2	2.0
Lawyer			1	2.0	1	2.0	2	2.0
Unemployed			2	4.0	7	14.0	9	9.0
Student			-	-	1	2.0	1	1.0
Economist			5	10.0	6	12.0	11	11.0
Worker			2	4.0	3	6.0	5	5.0
Teacher			8	16.0	3	6.0	11	11.0
Total			**50**	**100.0**	**50**	**100.0**	**100**	**100.0**

At baseline, we found no statistically significant difference (Fig. 2a, U'=1470.5, $P=0.127$) in the VAS scores between groups, indicating that the disease activity was similar between the two groups in the present study. This finding suggests that the initial pain levels and, by extension, the disease activity were comparable between the two groups, confirming that the randomization process effectively balanced this clinical variable at the start of the study. However, after six months, a statistically significant difference was identified between the groups (Fig. 2b, U'=2245.5, $P<0.0001$). The pain level was significantly lower in the vitamin D group than in the control group, indicating the positive effect of vitamin D on the progression of RA disease in relation to pain levels. The results support the potential role of vitamin D as an adjunctive treatment in RA management aimed at improving patient quality of life.

There was no significant difference in the mean DAS-28 score between the study groups at baseline (Fig. 3a, U'=1431.5, $P=0.212$). However, after six months of supplementation with vitamin D, a statistically significant difference between the two groups was observed (Fig. 3b, U'=2285.5 $P<0.0001$). In this regard, the DAS-28 score was significantly lower in the vitamin D group, indicating less inflammation and disease activity in RA patients and an improved clinical condition.

To evaluate the effect of vitamin D therapy on disease activity, prior to the intervention, we measured the levels of inflammatory mediators in both groups. There were no differences in the levels of inflammatory mediators, including IL6 (H statistic of 1.79 for p.180), IL17 (H statistic of 0.015 for p.902), TNF (H statistic of 1.15 for p.284), ESR (H statistic of 0.085 for p.771) or CRP (H statistic of 1.45 for p.29), between the groups at baseline. This means that both groups had similar inflammation levels before the intervention, ensuring a fair comparison when evaluating the effect of vitamin D on disease activity later in the study. Further details are provided in Table 3.

Moreover, linear regression analysis was conducted to assess the effect of Vitamin D supplementation on clinical outcomes. Specifically, a linear regression was

Table 2 Clinical characteristics of the RA patients ($n=100$)

First symptoms of RA (Years)	**Gr. W/Vit. D**		**Gr. WO/Vit. D**		**Total**		**Mann–Whitney test**
N	50		50		100		U' = 1329.5,
Mean	7.7		8		7.8		$P=0.585$
SD	3.4		3.3		3.4		
Min	1		1		1		
Max	14		14		14		
Diagnoses of RA (Years)	**Gr. W/Vit. D**		**Gr. WO/Vit. D**		**Total**		***T test*, *P*value**
N	50		50		100		t = 0.335, $P=0.738$
Mean	7.3		7.5		7.4		
SD	3.3		3.3		3.3		
Min	1		1		1		
Max	14		13		14		
Localization of damaged joints	**Gr. W/Vit. D**		**Gr. WO/Vit. D**		**Total**		**Fisher test**
	N	**%**	**N**	**%**	**N**	**%**	
4–10 small joints (large joints do not count)	2	4	3	6	5	5	$P=1.00$
> 10 joints (at least one a small joint)	48	96	47	94	95	95	
Total	**50**	**100**	**50**	**100**	**100**	**100**	
Extra-articular manifestations	**Gr. W/Vit. D**		**Gr. WO/Vit. D**		**Total**		**Chi test**,
	N	**%**	**N**	**%**	**N**	**%**	**P value**
Total	**50**	**100**	**50**	**100**	**100**	**100**	Chi = 0.313,
Carpal tunnel syndrome	4	8	4	8	8	8	$P=0.997$
Vasculitis	1	2	1	2	2	2	
Scleritis	1	2	2	4	3	3	
Neuropathy	6	12	6	12	12	12	
Dry eyes	6	12	6	12	12	12	
Dry mouth	6	12	6	12	12	12	
Serological test	**Gr. W/Vit D**		**Gr. WO/Vit. D**		**Total**		**Chi test**,
	N	**%**	**N**	**%**	**N**	**%**	**P value**
Negative RF and negative ACPA 0	9	18	9	18	18	18	Chi = 0.213, $P=0.899$
Low positive RF or low positive ACPA 2	2	4	3	6	5	5	
High positive RF or high positive ACPA 3	39	78	38	76	77	77	
Total	**50**	**100**	**50**	**100**	**100**	**100**	
Serum 25(OH) levels ng/mL in baseline							
Gender	**Comparison**		**Mean Difference (MD)**		**t test**	**P = value**	**Significance**
Male	**Gr. W/Vit D vs. Gr. WO/ Vit. D**		15.08-15.00 = 0.08		0.1	0.92	No significant
Female			15.29 – 16.70 = – 1.41		-2.2	0.03	Significant

performed with the change in DAS-28 score (from baseline to 6 months) as the dependent variable, adjusting for age, gender, baseline DAS-28, and disease duration. Table 4 shows that vitamin D supplementation was associated with a statistically significant reduction in DAS-28 score ($\beta = -1.172$, $p<0.01$). This indicates that, on average, patients who received vitamin D experienced greater clinical improvement over the 6 months. Similarly, a regression model using the change in CRP (from baseline to 6 months) as the dependent variable showed that vitamin D supplementation was significantly associated with a greater reduction in CRP levels ($\beta = -8.257$, $p<0.01$), independent of age, gender, initial CRP levels, and disease duration.

Our results show that vitamin D supplementation was a significant independent predictor of improvement. Participants in the treatment group experienced an average reduction of 1.17 points in DAS-28 ($\beta = -1.172$, $p<0.01$) and a decrease of 8.26 mg/L in CRP ($\beta = -8.257$, $p<0.01$), compared to controls.

Among the control variables, baseline values were strong and significant predictors in both models. Patients with higher initial DAS-28 or CRP levels tended to experience greater reductions over time, consistent with a regression-to-the-mean pattern. Gender was significantly associated with CRP change ($\beta = 4.669$, $p<0.05$), with men showing larger reductions than women, while it had no significant effect on DAS-28 change. Age and

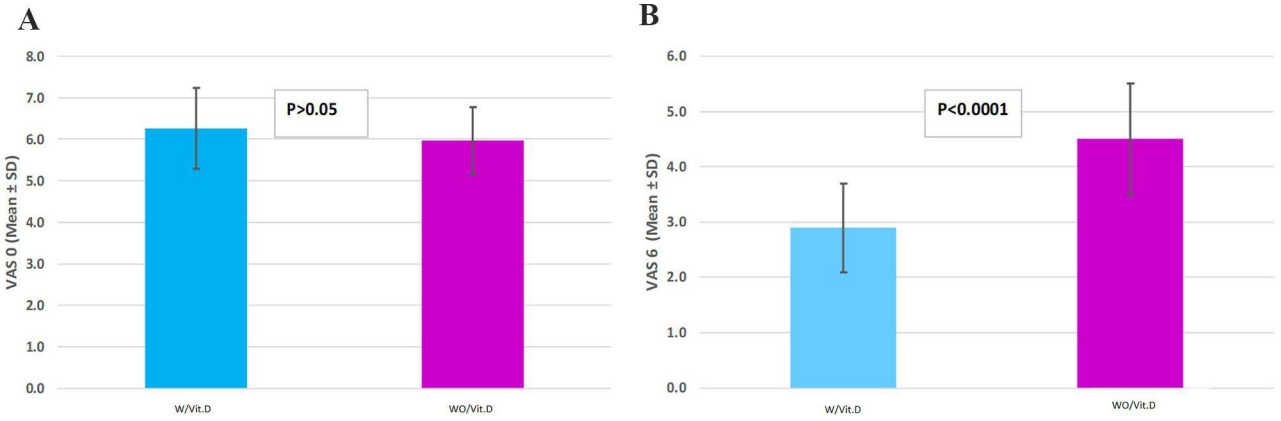

Fig. 2 (**a**) Mean VAS score between vitamin D group and control group at baseline; (**b**) after 6 months

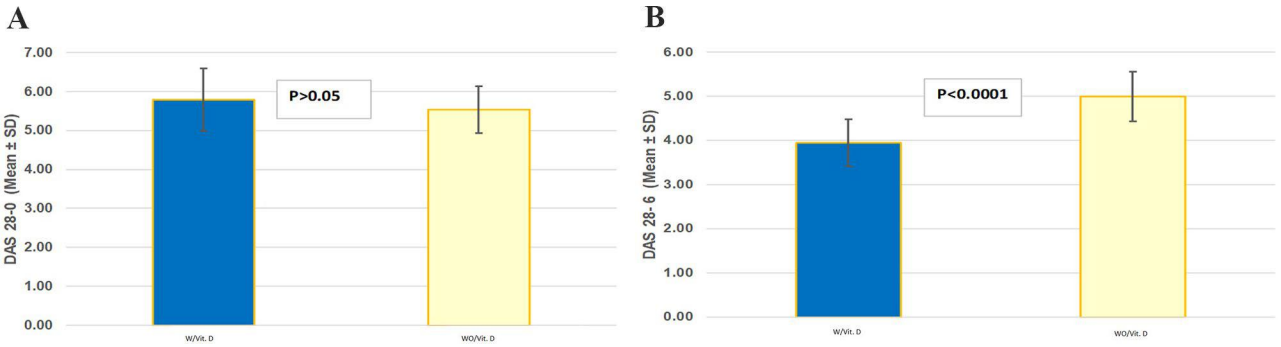

Fig. 3 (**a**) Mean DAS between vitamin D group and control group at baseline; (**b**) after 6 months

Table 3 Pairwise kruskal–wallis test of inflammatory mediators between patients with and without vitamin D

Inflammatory mediators in RA	Group of RA patients	Baseline		
		H-statistic	*p* value	Significance ($p < 0.05$)
IL6	With Vitamin D	1.79	0.180	$p \geq 0.05$
	W/O Vitamin D			
IL17	With Vitamin D	0.015	0.902	$p \geq 0.05$
	W/O Vitamin D			
TNF	With Vitamin D	1.15	0.284	$p \geq 0.05$
	W/O Vitamin D			
SE	With Vitamin D	0.085	0.771	$p \geq 0.05$
	W/O Vitamin D			
CRP	With Vitamin D	1.45	0.29	$p \geq 0.05$
	W/O Vitamin D			

No adverse events, side effects, or unintended negative effects were observed or documented in either the treatment or control group throughout the duration of the trial

Table 4 Linear regression

Variables	(1)	(2)
	Change in DAS-28	Change in CRP
vitD_group	-1.172***	-8.257***
	(0.083)	(1.815)
Age	-0.006	-0.055
	(0.008)	(0.161)
Gender	-0.103	4.669**
	(0.101)	(2.187)
das28_0	-0.445***	-0.731***
	(0.056)	(0.036)
duration_of_diagnosis	-0.022*	-0.148
	(0.012)	(0.274)
Constant	2.413***	14.089*
	(0.435)	(7.988)
Observations	100	100
R-squared	0.798	0.844

Standard errors in parentheses

*** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$

duration of diagnosis were not significant in the CRP model, and duration showed only a weak association with DAS-28 change ($\beta = -0.022$, $p < 0.1$).

Table 5 presents that these effects are clinically meaningful: a reduction of at least 1.2 points in DAS-28 indicates a moderate to good treatment response. At the same time, an 8.26 mg/L drop in CRP represents a substantial reduction in systemic inflammation. Overall, our findings suggest that vitamin D supplementation has a robust and clinically relevant impact on disease activity and inflammation in RA patients, independent of demographic and disease-related factors.

Table 5 Effect of vitamin D on change in DAS-28 and CRP

Outcome	Coefficient (β)	Std. Error	*p*-value	Interpretation
DAS-28 change	−1.172	0.083	< 0.01	Significant reduction in disease activity
CRP change	−8.257	1.815	< 0.01	Significant reduction in inflammation

Models adjusted for age, gender, baseline values, and disease duration

*** $p < 0.01$

Discussion

The main aim of our study was to evaluate the effect of vitamin D in patients with RA by examining pain levels and the clinical course of the disease at baseline and after six months. The randomization of patients at the beginning of the study ensured a homogeneous distribution of patients and prevented any bias or external influences. The results revealed no significant differences in 25(OH)D levels or the levels of the inflammatory mediators IL6, IL17, CRP, ESR and TNF-α between the study groups prior to vitamin D supplementation. Vitamin D supplementation plays an important role in improving disease activity and reducing pain levels over a 6-month period. These findings have important clinical implications for the management of RA patients, especially with respect to the selection and dosing of pharmacotherapy employed to control disease activity and pain levels over time [20, 21].

Our findings confirm the findings of previous studies on the relationships of vitamin D deficiency with disease activity and pain. In this context, Haque et al. reported that vitamin D deficiency was linked to higher DAS-28 scores and pain levels [22]. Similarly, Mukherjee et al. reported that supplementation with 60,000 IU/week has a positive effect on reducing pain levels [23]. In comparison, our study achieved this same positive effect with a lower dose of 4000 IU/day. This finding could have implications for treatment adherence and the ongoing use of vitamin D supplementation, especially in regard to the selection of dosage and form of vitamin D administration. Our results revealed a lower DAS28 score in the vitamin D group than in the study group without vitamin D in the period after six months, indicating the positive effect of vitamin D supplements on disease activity and control. This analysis also revealed an improvement in joint swelling and tenderness in RA patients and a decrease in the ESR. Although other studies have shown that vitamin D does not significantly reduce DAS28 levels in patients with RA, some studies have emphasized the important effect of vitamin D in lowering DAS28 [9, 24, 25].

The incidence of RA in women was almost four times higher than that in men, and this ratio is consistent with some results from other studies [26]. The predominance of female patients with RA (86.0%) in the overall cohort of the study by randomization was almost equally distributed in both groups, with no significant differences. The 50–59 years age group was more represented in the vitamin D group, whereas the 40–49 years age group was in the group of patients without vitamin D. This did not have a confounding effect on the results of the study. However, previous studies have suggested that significant age differences in RA patients have an important influence on the course of the disease and the effectiveness of the treatment [27, 28].

To examine and compare the disease characteristics between the study groups, we also evaluated the average duration of disease in years in relation to the onset and duration of RA. Our results revealed that the mean duration of disease onset was not significantly different between the two groups (vitamin D group vs. control group = 7.3 years and 7.5 years, respectively). This was also the case for the mean time of disease diagnosis in the two groups (7.7 years vs. 8.0 years). These findings suggest that at baseline, there were similar disease conditions among both groups, thereby mitigating the risk of bias [29].

In addition to the clinical features of the disease, we also analysed the presence of extra-articular manifestations in both study groups. The most common extra-articular manifestations of RA were neuropathy, followed by carpal tunnel syndrome, ocular dryness, dry mouth, vasculitis and scleritis; there were no differences in these symptoms between the two groups. This approach aimed to determine the equal distribution of clinical features between subjects in both study groups, and it was not intended to investigate the effect of vitamin D on the frequency and severity of extra-articular manifestations. In this context, a larger sample of patients and a longer study duration are needed to demonstrate the possible effects of vitamin D on extra-articular manifestations and disease activity [30, 31].

In addition to this, pre-menopausal women with low levels of 25(OH)D3 more frequently experience Fibromyalgia Syndrome and pain [25].

The improvement in disease course and pain support the selectivity of vitamin D in specific immunomodulatory cascades and inflammatory mechanisms, although we cannot discern the general effect of vitamin D in immunomodulation RA pathophysiology. Other studies have shown the influence of vitamin D on decreasing IL6 levels in RA patients, although some studies have reported contrasting results [27, 32]. We assume that the clinical improvement observed among RA patients who received vitamin D supplementation compared with the control group was due to the modulatory effects of vitamin D on the inflammatory mediators of disease [28]. This modular effect of vitamin D may result in reduced

systemic inflammation and improved clinical conditions [10, 33].

Recent studies reported research about the relationship between inflammation-based nutritional score and disease activity in RA patients [30] which could benefit for future investigations. Moreover, there is evidence showing the relationship between low prognostic index and high disease activity [34]. In line with our empirical results, according to Song et al., a higher vitamin D level is linked to a decreased chance of developing RA [35]. This finding supports previous research showing a negative correlation between vitamin D and DAS 28 [36, 37]. Another study concluded that as a measure of RA patients' disease activity and the effectiveness of vitamin D following medication treatment, the DAS28 score is highly significant, which means that vitamin D administration successfully decreased the DAS28 score of rheumatoid arthritis patients [38]. Also, some studies conclude a decrease in CRP levels for the group with Vitamin D supplementation. However, no significant difference was found between the levels in the control group [39, 40]. It can be concluded that Vitamin D supplementation appeared to be a successful treatment for RA patients.

Limitations of study

There are several limitations that should be taken into account when our findings are interpreted. Considering that RA is a chronic remitting disease, we consider the follow-up period of 6 months to be relatively short to evaluate the long-term effect of vitamin D; thus, longer follow-up periods beyond 6 months are needed to assess the constant impact of vitamin D on disease activity and remission rates. We had only two study groups, with and without vitamin D, and we expect that more study groups with different doses and larger sample size may provide better insights into the effects of vitamin D on disease activity. Nevertheless, studies with multiple dosage groups could provide insights into the optimal therapeutic levels of vitamin D for RA patients.

The control group did not receive the placebo capsule, and the absence of the placebo may have limited the ability to maintain blinding. Due to the limited resources and non-commercial nature of the project, it was not technically feasible to manufacture or supply placebo tablets. The inclusion of a placebo control would have strengthened the internal validity of the study and we consider this to be an important point that should be addressed in future research with appropriate logistical and financial support.

It is suggested that future research should incorporate more objective measures of pain and disease activity, along with patient-reported outcomes, to improve the accuracy of the findings. Furthermore, we did not account for potential confounding effects of other medications that patients were taking as standard therapy. Standard RA medications –vitamin D interactions might have affected our findings and hence their potential effects on vitamin D levels [41] and this should be investigated. Concomitant treatments may have influenced both disease activity and vitamin D metabolism. Considering that we measured the inflammatory mediators of the disease only at baseline, assessing these mediators at multiple time points might provide a clearer understanding of the impact of vitamin D on inflammation in RA. Monitoring the inflammatory markers (IL-6, IL-17, CRP, TNF-α, ESR) at different time points of patients with RA, would allow a more inclusive understanding of the immunological effects of vitamin D in RA patients and better annotate its therapeutic potential.

Conclusions

In conclusion, our findings suggest that 4000 IU/day of vitamin D supplementation has positive effects on the clinical outcomes of patients with RA and emphasize the potential beneficial effects of high-dose vitamin D supplementation (4000 IU/day) in patients undergoing stable RA protocol therapy. This approach highlights the role of adjunctive vitamin D therapy in this specific clinical category of RA patients. Furthermore, we observed improvements in disease activity and pain in RA patients after 6 months of treatment and further research is needed to validate the long-term effects and to elucidate the specific role, underlying mechanisms, and safety of vitamin D supplementation in RA patients. Specifically, extended follow-up of the immunomodulatory effects of vitamin D in RA is essential to clarify its impact on improving patient outcomes and quality of life for individuals living with RA. Screening for vitamin D levels can help identify patients at risk for more severe disease, allowing for early intervention with vitamin D supplementation if necessary. This could potentially reduce the inflammatory burden and improve patient outcomes.

Abbreviations

25(OH)D	25-hydroxyvitamin D
ACPA	Anti-citrullinated peptide antibodies
CRP	C-reactive protein
DAS28	Disease Activity Score-28
ESR	Erythrocyte sedimentation rate
IL17	Interleukin-17
IL6	Interleukin-6
RA	Rheumatoid Arthritis
RCT	Randomized controlled trial
RF	Rheumatoid factor
TNF-α	Tumour necrosis factor alpha
VAS	Visual analogue scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41927-025-00543-6.

Supplementary Material 1

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Not applicable.

Author contributions
M.R. and Sh.K. designed and analysed the data; M.R. conducted the clinical trial; A.D., B.K., B.R.K. conducted the data collection and statistical analysis; Sh.K. and K.H. reviewed the results and wrote the article.

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Data availability
Data is provided within the manuscript as a supplementary document. As stated in the Data availability statament, the datasets generated and/or analysed during the current study are not publicly available to protect the privacy and confidentiality of study participants. As the study involves sensitive patient data, it is securely maintained by the main author, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethics Committee, Statement number 2598, of the Faculty of Medicine, University of Prishtina. Patients were only included in the study after they signed the informed consent form and were fully informed about the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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