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Review article

Effect of vitamin D supplementation on patients with systemic lupus erythematosus: a systematic review

Joyce Ramalho Sousa[a], *Érica Patrícia Cunha Rosa*[a], *Ivone Freires de Oliveira Costa Nunes*[b,*], *Cecilia Maria Resende Gonçalves de Carvalho*[b]

[a] *Faculdade Santo Agostinho (FSA), Teresina, PI, Brazil*
[b] *Universidade Federal do Piauí (UFPI), Teresina, PI, Brazil*

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ABSTRACT

The objective of this systematic review was to analyze clinical trials carried out for the investigation of the effect of vitamin D supplementation on systemic lupus erythematosus. The research was performed from August to September 2016, without limits regarding year of publication, restriction of gender, age, and ethnicity. For the guiding question, the PICO strategy was employed. To evaluate the quality of the publications the PRISMA protocol and Jadad scale were used. The risk of bias analysis of the clinical trials was performed using the Cochrane collaboration tool. After the process of article selection and removal of duplicates, four articles were identified as eligible. The results of three studies showed a positive effect of supplementation on disease activity reduction and significant improvement in levels of inflammatory markers, fatigue, and endothelial function. Only one study showed no improvement in disease activity after supplementation. Moreover, all studies showed an increase in serum vitamin D levels. The data from this review provide evidence on the benefits of vitamin D supplementation in patients with lupus and vitamin D insufficiency/deficiency. However, it is still necessary to elucidate whether vitamin D acts in the protection against this metabolic disorder, as well as the standardization of the type, dose and time of vitamin D supplementation.

* *Corresponding author.*
E-mail: ivonefreirescosta@ufpi.edu.br (I.F. Nunes).

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Efeito da suplementação com vitamina D em pacientes com lúpus eritematoso sistêmico: uma revisão sistemática

Palavras-chave:
Vitamina D
Lúpus eritematoso sistêmico
Suplementação
Revisão sistemática

RESUMO

O objetivo desta revisão sistemática foi analisar ensaios clínicos realizados na investigação do efeito da suplementação com vitamina D sobre o lúpus eritematoso sistêmico. A pesquisa foi realizada nas bases de dados Scopus, PubMed e Biblioteca Cochrane, no período de agosto a setembro de 2016, sem limite de ano de publicação, restrição de gênero, idade e etnicidade. Para a questão norteadora foi empregada a estratégia PICO. Para avaliar a qualidade das publicações utilizou-se o protocolo PRISMA e a escala de Jadad. A análise do risco de viés dos ensaios clínicos ocorreu pela ferramenta de colaboração Cochrane. Após o processo de seleção e remoção de artigos duplicados, quatro artigos foram identificados como elegíveis. Os resultados de três estudos mostraram efeito positivo da suplementação na redução da atividade da doença e melhora significativa nos níveis de marcadores inflamatórios, fadiga e função endotelial. Em apenas um estudo não houve melhora na atividade da doença após a suplementação. Ademais, todos os estudos apresentaram aumento dos níveis séricos de vitamina D. Os dados dessa revisão fornecem evidências dos benefícios da suplementação com vitamina D sobre o lúpus em pacientes com insuficiência/deficiência. Contudo, ainda é necessário elucidar a atuação do nutriente na proteção contra esse distúrbio metabólico, bem como a padronização do tipo, dose e tempo de suplementação com vitamina D.

Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune inflammatory disease that affects several organs and systems of the body. Its cause and epidemiology are unknown, since a combination of factors, including ethnicity, gender, genetic and environmental aspects are involved. The disease affects 30–50/10,000 individuals worldwide, most frequently affecting young women of reproductive age, affecting 10–12 women for each man.[1,2]

Recent studies have highlighted the role of vitamin D in the development of autoimmune diseases. Vitamin D deficiency seems to be associated with SLE activity, partly due to dysregulation in cytokine production balance. The photosensitivity and recommendation of sunscreen use, as well as other measures for less sun exposure, may favor the reduction of cutaneous vitamin D synthesis.[3]

Therefore, due to the importance of the vitamin D-SLE binomial, the aim of this review was to evaluate the effects of vitamin D supplementation on systemic lupus erythematosus, contributing to the increase of knowledge based on scientific evidence, considering that the subject is relevant, new and, therefore, requires more discussion to adequately guide the decision-making by health professionals.

Methods

A Systematic Review (SR) of studies on vitamin D supplementation in patients with Systemic Lupus Erythematosus was performed. The PICO strategy was used to establish the guiding question of the present study, which represents the acronym for problem or population (P), intervention (I), comparison (C) and outcome (O). These four components are the fundamental elements of the research question and of the question construction for the bibliographic search for evidence.[4] This strategy culminated in the definition of the following guiding question: Does vitamin D supplementation lead to clinical improvement in SLE patients? Each PICO domain corresponded to the following elements: (P) Patients with systemic lupus erythematosus, (I) Vitamin D supplementation, (C) Placebo and (O) clinical improvement of SLE patients.

The search was carried out in the Scopus, PubMed, and Cochrane Library databases for published clinical trials with no limit regarding year of publication, and no restriction regarding gender, age, and ethnicity, all published in the English language. The Boolean connector “and” was used in the combination of the Medical Subject Heading (MeSH) terms: systemic lupus erythematosus and clinical trial, vitamin D and supplementation and vitamin D and supplementation and clinical trial.

The titles and abstracts of the selected articles were analyzed to verify whether they met the inclusion criteria: having a controlled clinical trial design and being available as a full-text article. The evaluation of the eligibility criteria was performed independently by the two authors, and in case of divergence, a third researcher was consulted.

To ensure the SR quality, the Preferred Reporting Items for Systematic Reviews, and Meta-Analyses (PRISMA) protocol was used.[5] The Jadad scale[6] was used independently by two blinded researchers for the qualitative classification. Scores were assigned to the studies (from zero to five), based on the criteria: randomization method (sequences and randomization criteria of participants), blinding (for patients and researchers) and description of follow-up loss proportion. The risk of bias in the clinical trials included in this study was identified through the Cochrane Collaboration Tool.[7]

Table 1 – Analysis of the methodological quality and risk of bias proposed by the Cochrane collaboration.

Variables	Abou-Raya et al.[8] (2013)	Aranow et al.[9] (2015)	Kamen; Oates[10] (2015)	Lima et al.[11] (2016)
Random sequence generation	Uncertain	Uncertain	Low risk	Uncertain
Allocation concealment	Low risk	Low risk	Low risk	Low risk
Blinding of participants and personal	Low risk	Low risk	Low risk	Low risk
Blinding of outcome evaluators	Low risk	Low risk	Low risk	Low risk
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk
Selective outcome reporting	Low risk	Low risk	Low risk	Uncertain
Other sources of bias	Low risk	Low risk	Low risk	Low risk

Results

The bibliographic search, carried out according to the pre-established strategy, resulted in 25 articles. Of these, seven studies were from the Scopus database, eight from PubMed and ten from Cochrane. After the selection and removal of articles in duplicate, four original articles from randomized controlled trials (RCTs) were identified as eligible for this systematic review. Fig. 1 shows the flowchart of the search result in the information sources, the selection and inclusion of the original articles in the Systematic Review, according to the PRISMA statement protocol.

The clinical trials showed homogeneous methodological quality based on bias risk assessment using the Cochrane tool (Table 1). Randomization was adequately reported in 25% (1/4) of the studies, while allocation sequence generation, blinding of outcome evaluators, blinding of participants and professionals, incomplete outcomes, and other sources of bias showed 100% (4/4) of low risk and selective outcome report showed 75% (3/4) of low risk. Table 2 shows the results of the quality evaluation of articles analyzed according to Jadad scale. In relation to the assessed items, all articles adequately described the aspects assessed in the aforementioned scale.

Table 2 – Evaluation of the clinical trials using the Jadad scale.

Author (year)	Score
Abou-Raya et al.[8] (2013)	5 points
Aranow et al.[9] (2015)	5 points
Kamen and Oates[10] (2015)	5 points
Lima et al.[11] (2016)	5 points

The data shown in Table 3 encompass the results of the reviewed articles, including authors, year of publication, geographic location, study sample size, dose, duration of supplementation and main outcomes. It was observed that clinical trials were carried out in different countries. Doses of vitamin D supplementation ranged from 400 IU to 500,000 IU, and the duration of the intervention lasted from 12 weeks to one year.

The main variables investigated were: changes in levels of pro-inflammatory cytokines and homeostatic markers, IFNα gene expression, urinary calcium levels, creatinine and parathormone (PTH) levels, endothelial function, fatigue and disease activity, and serum levels of vitamin D.

The results of the four clinical trials showed that vitamin D supplementation increased serum vitamin levels. Three

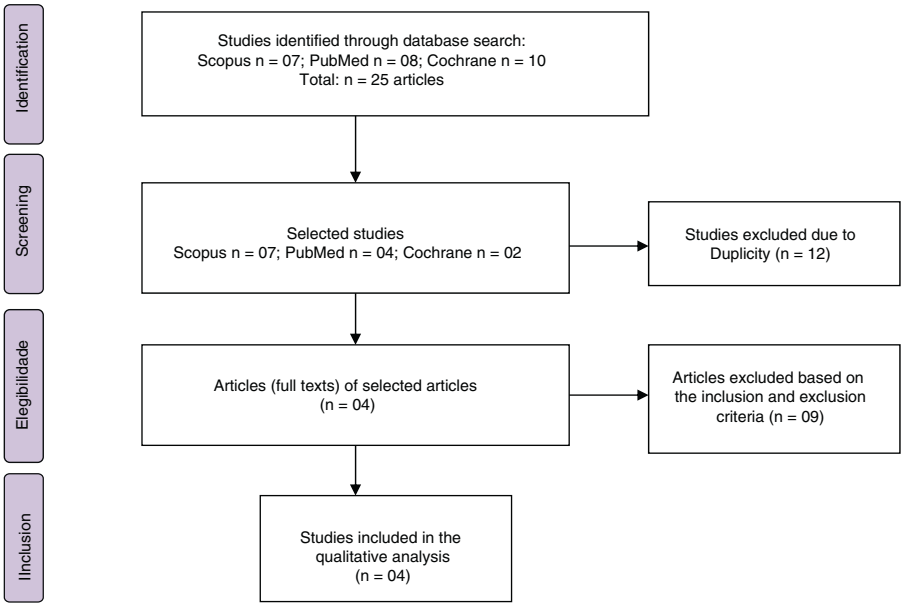

Fig. 1 – Flowchart of the search results in the accessed databases, screening, eligibility, and inclusion of articles in the systematic review.

Table 3 – Summary of the included studies regarding the effect of vitamin D supplementation on SLE.

Authors/year/country	Sample	Assessed variables	Intervention	Outcomes
Abou-Raya et al.[8] 2013 Egypt	$n = 267$	• Levels of 25(OH)D. • Changes in pro-inflammatory cytokines and hemostatic markers. • Improvement in disease activity before and after supplementation.	• Randomization: 2:1 (2000 IU/day of oral cholecalciferol or placebo). • Duration: 12 months.	• Improvement in inflammatory and hemostatic markers, and disease activity in the treatment group when compared to the placebo group ($p < 0.05$).
Aranow et al.[9] 2015 United States	$n = 57$	• Gene expression (IFNα). • Levels of 25(OH)D, urinary calcium, and parathyroid hormone (PTH) measured at the beginning and end of the study. • Creatinine levels at the start, at 6 and 12 weeks.	• Randomization: 1:1:1. • Placebo, 2000 IU (low dose), or 4000 IU (high dose) of vitamin D3 by oral administration. • Duration: 12 weeks.	• Increased mean levels of 25(OH)D throughout time. • Placebo: Levels of 25(OH)D remained stable. • Supplementation with vitamin D3-4000 IU/day did not decrease gene expression of IFNα.
Kamen; Oate.[10] 2015 United States	$n = 16$	• Levels of 25(OH)D. • Endothelial function: flow-mediated dilation (FMD) before and after vitamin D3 supplementation.	• Randomization: 1:1. • (Control: 400 IU of vitamin D3/day; Treatment: 5000 IU/day). • Duration: 16 weeks.	• Tendency of increases in FMD in individuals treated with 5000 IU/day compared to controls ($p < 0.05$). • Those who had increased FMD had greater changes in 25(OH)D levels.
Lima et al.[11] 2016 Brazil	$n = 40$	• Levels of 25(OH) D. • Disease activity. • Fatigue.	• Randomization: 1:1 (50,000 IU/week of oral cholecalciferol and placebo). • Duration: 24 weeks.	• Decreased disease activity. • Improved fatigue.

studies showed a positive effect of supplementation on disease activity and a significant improvement in levels of inflammatory markers, fatigue, and endothelial function. Only one study showed no improvement in disease activity after supplementation.

Discussion

Most of the clinical trials included in this review found improvement in serum vitamin D levels and the parameters involved with SLE.[8,10,11] Abou-Raya et al.[8] studied patients with SLE randomized 2:1 to receive 2000 IU of oral cholecalciferol per day or placebo for 12 months. At the end of the treatment, 25(OH)D levels were increased. The supplemented group showed a mean of 37.8 ± 16.3 ng/mL compared to the placebo group, with 19.9 ± 16.2 ng/mL ($p < 0.05$). Moreover, there was a significant improvement in the levels of inflammatory and hemostatic markers, as well as in the disease activity score measured by SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), in which patients with vitamin D deficiency had a worse SLEDAI score.

In the study by Kamen and Oates,[10] the participants were randomized 1:1 to receive 1 of 2 daily oral doses of vitamin D3. Group 1 (control) received 400 IU of vitamin D3 daily and Group 2 (treatment) received 5000 IU. At the end of the experiment, there was an improvement in endothelial function in supplemented patients when compared to controls, with a significant increase trend in the FMD (flow-measured dilation). Those who had an increase in FMD had significantly greater changes in 25(OH)D levels, i.e., it was observed that the higher the vitamin D level, the higher the FMD ($p < 0.05$).

Lima et al.[11] measured serum levels of 25(OH)D, assessed disease activity and fatigue for a period of 24 weeks in patients with juvenile-onset SLE, who were randomized (1:1) to receive oral cholecalciferol, 50,000 IU/week or placebo. After the intervention, it was observed that supplementation with cholecalciferol was effective in reducing disease activity and improving fatigue in patients with juvenile SLE. Disease activity was assessed by SLEDAI. Fatigue scores, including low-intensity fatigue, fatigue during exercise, and fatigue at medium effort, were significantly lower in patients supplemented with vitamin D ($p < 0.05$).

However, Aranow et al.,[9] when assessing 57 North-American women with SLE, randomized 1:1:1 to receive 2000 IU (low dose), 4000 IU (high dose) of vitamin D3, or placebo orally per day for 12 weeks, found that vitamin D values remained stable (30 ng/mL) in patients receiving placebo and low dose. The high dose group achieved slightly higher levels (30–35 ng/mL). However, no effect was obtained regarding the decrease in IFNα gene expression, and no significant correlations were found between vitamin D supplementation and SLE disease activity ($p > 0.05$). Additionally, there was no correlation between 25(OH)D and changes in gene expression.

It is emphasized that a daily consumption of 4000 IU of vitamin D3 was considered safe and well tolerated, with no signs of toxicity. Cases of hypercalcemia were mild and infrequent. An unexpected fact was also observed, characterized by a decrease in neutrophils, which was not associated with adverse effects.[9]

Moreover, it is worth noting the study by Andreoli et al.,[12] which showed that in SLE patients during a one-year supplementation with cholecalciferol receiving either the standard regimen (25,000 IU/month) or the intensive regimen (initial

bolus of 300,000 IU, followed by 50,000 IU monthly), the latter (with high dose of vitamin D) was safe and effective in attaining sufficient vitamin levels (>30 ng/mL). However, both supplementation regimens showed no difference in the way they affected disease activity as assessed by SLEDAI, or the serology for SLE ($p > 0.05$).

In another study, Ruiz-Irastorza et al.[13] when they performed a longitudinal observational study with 47 patients with SLE who received 800 IU/day of vitamin D3 during a mean period of 24 months (range 5–24 months) and another 10 who received 600 IU/day during the 24-month period (range 7–24 months) found at the end of the experiment that 25(OH)D levels increased in all treated patients. The mean levels of 25(OH)D increased from 21.7 ng/mL to 24.8 ng/mL; however, there was no improvement in SLE activity. The same authors recommend the use of vitamin D3 at higher doses than 800 IU/day for patients with SLE and vitamin D insufficiency or deficiency.

In the study by Reynolds et al.,[14] oral cholecalciferol supplementation (400,000 IU followed by 20,000 IU weekly) in patients with vitamin D deficiency positively modulated endothelial function in individuals with stable SLE, regardless of disease activity. These observations support a role for vitamin D in cardiovascular health improvement, by reducing the risk of this disease in SLE.

The results by Petri et al.[15] when assessing 763 North-American patients with a mean age of 49.6 ± 13.2 years with SLE, observed that individuals with low levels of 25(OH)D supplemented with 50,000 IU of vitamin D2 weekly and with 200 IU of Ca/D3, twice a day for 128 weeks had a modest, but significant reduction in the risk of increased disease activity ($p < 0.05$) and also an association with 25(OH)D increase in the subset of patients with low vitamin D levels.

Terrier et al.[16] found an important increase in 25(OH)D serum levels and regulatory T-cells in 20 French patients with hypovitaminosis D, whose mean age was 31.0 ± 8.0 years included in the supplementation program with 100,000 IU cholecalciferol/4 weeks, followed by 100,000 IU cholecalciferol/month for 6 months. There was also a decrease in memory B cells and effector T cells (Th1 and Th17), thus being effective in inducing an immunomodulatory effect in lupus.

In parallel, the participation of anti-vitamin D antibodies in the metabolic process of vitamin D is emphasized, especially because they are associated to the capacity to contribute to their clearance by the body. In the study by Carvalho et al.[17] 171 patients with lupus were evaluated and anti-vitamin D antibodies were present in 4% of the sample. As for 25(OH)D levels, there was no statistically significant difference when comparing those with (28.4 ± 9.6 ng/mL) and without (26.4 ± 13.9 ng/mL) ($p > 0.05$) autoantibodies.

Moreover, this same study[17] found that the presence of anti-DNA double-stranded antibodies (anti-dsDNA) was the only one that showed a strong association with anti-vitamin D antibodies, suggesting that these antibodies, even though they were found at low frequency, may imply in reduced serum levels of vitamin D. However, further analysis is needed on the potential diagnostic and prognostic role of these new antibodies in SLE.

It is noteworthy that there was a discrepancy regarding the doses and time of supplementation used in the studies analyzed in this review. The studies were carried out in different populations, which may have contributed to the divergences of the identified results.

Conclusions

The results of this study showed that vitamin D supplementation, in most publications, improved serum vitamin D levels, disease symptoms and complications, with significant improvement in the levels of inflammatory markers, fatigue, and endothelial function.

The results of this review provide evidence of the benefits of vitamin D supplementation in individuals with SLE and vitamin D deficiency/insufficiency. However, further intervention studies are required to verify a more effective therapy to protect the body from the deleterious effects of this autoimmune disorder.

Conflicts of interest

The authors declare no conflicts of interest.

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