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## **Can vitamin supplementation improve quality of life and disease severity in patients with rheumatoid arthritis, or is physical activity enough?**

### 1. Michał Andrzej Kozicz [MAK]

Brothers Hospitallers Hospital in Kraków, Trynitarska 11, 31-061 Kraków, Poland

<https://orcid.org/0009-0001-4254-4087>

[kozicz.michal@gmail.com](mailto:kozicz.michal@gmail.com)

### 2. Paulina Cuper [PC]

Brothers Hospitallers of Saint John of God Hospital in Cracow; Trynitarska 11 Street, 31-061

Kraków, Poland;

<https://orcid.org/0009-0007-5386-4338>

[cuperpaulina@gmail.com](mailto:cuperpaulina@gmail.com)

### 3. Ilona Jastrzębska [IJ]

Grochowski Hospital, Grenadierow 51/59 Street, 04-073 Warsaw, Poland

<https://orcid.org/0000-0001-6754-529X>

[ilonaj14@gmail.com](mailto:ilonaj14@gmail.com)

4. Krzysztof Bilecki [KB]

SP ZOZ MSWiA, Kronikarza Galla 25, 30-053 Cracow, Poland

<https://orcid.org/0009-0001-8778-1422>

[kbilecki5@gmail.com](mailto:kbilecki5@gmail.com)

5. Hubert Gugulski [HG]

Jagiellonian University Medical College ul. Św Anny 12, 31-008 Kraków

<https://orcid.org/0009-0004-1294-9835>

[gugulski.hubert@gmail.com](mailto:gugulski.hubert@gmail.com)

6. Michał Bado [MB]

The University Hospital in Krakow, Jakubowskiego 2 Street, 30-688 Krakow, Poland

<https://orcid.org/0009-0008-6595-6560>

[michalbado@yahoo.com](mailto:michalbado@yahoo.com)

7. Patrycja Nowoświat [PN]

The University Hospital in Krakow, Jakubowskiego 2 Street, 30-688 Krakow, Poland

<https://orcid.org/0009-0008-7939-6621>

[patkano1998@gmail.com](mailto:patkano1998@gmail.com)

8. Michał Goncerz [MG]

Department of Anatomy - Jagiellonian University, Kopernika 12 Street, 31-034 Krakow,  
Poland

<https://orcid.org/0009-0003-8444-6922>

[michal.goncerz@uj.edu.pl](mailto:michal.goncerz@uj.edu.pl)

## **Abstract**

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation and progressive joint destruction, significantly impacting quality of life. While conventional treatments focus on managing symptoms and slowing disease progression through pharmacological means, the potential role of complementary therapies like vitamin supplementation or increased physical activity has garnered increasing interest.

Aim of the Study: This narrative review explores the existing literature on the efficacy and mechanisms of various vitamins in the management of RA. By synthesizing current research findings, we aim to provide a comprehensive overview of how vitamin supplementation might

influence RA outcomes, offering insights into potential integrative approaches to enhance patient care.

**Methods and Materials:** A thorough search was conducted using PubMed and Google Scholar, focusing on literature published in the past five years. Vitamins with potential impacts on RA progression were identified and paired with the term "Rheumatoid Arthritis" to collect data on their influence on the disease's incidence and management, as well as the mechanisms involved. Additionally, references from selected articles were reviewed and included in the analysis. This method ensured a comprehensive evaluation of the current evidence regarding vitamin supplementation in RA treatment. Similarly, studies on the impact of physical activity on RA were also reviewed.

**Results:** The influence of physical activity on serum inflammatory markers in RA patients was limited. Vitamin D supplementation significantly reduced disease activity, alleviated pain, and mitigated methotrexate-related side effects, especially in patients with baseline vitamin D deficiency or lower serum levels. In contrast, other vitamins have not exhibited the same positive effects. These findings underscore the need for continued research to optimize the role of various vitamins in managing RA effectively.

**Keywords:** Rheumatology, Rheumatoid arthritis, Physical Activity Quality of Life, Vitamin, Vitamin D

## **Introduction**

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease impacting approximately 1% of the world's population.<sup>1</sup> Although the exact cause of rheumatoid arthritis (RA) is unknown, it is considered a multifactorial disease arising from the interplay of genetic, hormonal, and environmental factors that lead to a loss of immune tolerance.<sup>1,2</sup> The diet has been highlighted for its role in influencing RA disease activity, as certain foods can either exacerbate or reduce inflammation.<sup>3,4</sup>

The disease significantly diminishes quality of life, leading to higher morbidity and reduced life expectancy. As the number of people with RA continues to grow, the economic burden on society has also increased substantially<sup>5,6</sup>, highlighting the need for effective management strategies to improve patient outcomes and mitigate societal costs. The economic burden affects not only society but also the patient, who bears the costs of treatment<sup>7</sup>. Consequently,

patients seek alternative or complementary treatment methods such as physiotherapy, acupuncture, physical activity, or dietary modifications.

While pharmacotherapy, physical activity and rehabilitation are well-known factors that improve the quality of life and general functioning of patients with rheumatoid arthritis<sup>1,8,9</sup>, dietary interventions and vitamin supplementation per se are still not widely recognized as an integral part of the therapeutical process<sup>10</sup>. Vitamin supplementation can be a valuable complement to conventional treatment regimens, potentially enhancing quality of life and reducing the frequency of disease flare-ups<sup>47</sup>.

This review aims to examine the role of supplementation in the treatment of RA. It will evaluate their potential benefits in managing the disease and reducing inflammation, providing a comprehensive overview of current evidence and identifying areas for future research.

### **Physical activity and quality of life in patients with rheumatoid arthritis**

Physical activity has proven effective in reducing disease activity<sup>8,11,12</sup>, alleviating pain<sup>13,14</sup>, fatigue<sup>15,16</sup>, and sleep disturbances in patients with rheumatoid arthritis.

This is also confirmed in a meta-analysis conducted by Björk et al. (2022) which encompassed 26 randomized controlled trials examining the impact of physical activity on rheumatoid arthritis. Compared to control groups, physical activity interventions significantly improved post-intervention outcomes in activity performance (SMD  $-0.25$ , 95% CI  $-0.37$ ;  $-0.13$ ,  $p < 0.001$ ), pain (SMD  $-0.24$ , 95% CI  $-0.43$ ;  $-0.05$ ,  $p < 0.05$ ), fatigue (SMD  $-0.28$ , 95% CI  $-0.49$ ;  $-0.08$ ,  $p = 0.006$ ), disease activity and symptoms (SMD  $-0.65$ , 95% CI  $-0.11$ ;  $-0.19$ ,  $p = 0.005$ ), and physical function (SMD  $-0.41$ , 95% CI  $-0.61$ ;  $-0.20$ ,  $p < 0.001$ ).<sup>17</sup>

Papandreou et al. (2023) investigated the combined impact of physical activity and the Mediterranean diet on the treatment of RA. After three months, patients who underwent the intensive lifestyle intervention showed a significant reduction in DAS28 compared to the baseline ( $p < 0.001$ ). No significant differences were found in CRP levels.<sup>18</sup>

However the influence of physical activity on serum inflammatory markers seems to be limited.<sup>19</sup> This indicates a knowledge gap in this area, suggesting the need for new research and the exploration of complementary solutions in the treatment of inflammatory joint diseases, such as oral vitamin supplementation.

## **Vitamin D**

Vitamin D, a nutrient of significant interest, has numerous immunosuppressive effects beyond its role in bone and calcium metabolism<sup>20</sup>. The active form of vitamin D, 1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>), interacts with vitamin D receptors (VDR)<sup>21</sup> on various cells, including osteoblasts, T cells, dendritic cells, macrophages, and B cells.<sup>22,22,28</sup> These cells can convert the more prevalent 25-hydroxyvitamin D<sub>3</sub> (25(OH)D<sub>3</sub>) into its active form, suggesting important autocrine and paracrine roles of vitamin D at sites of inflammation<sup>23</sup>.

Vitamin D inhibits the differentiation of monocyte precursors into mature dendritic cells driving differentiation towards macrophages<sup>24</sup>, down regulates expression of II MHC molecules on their surface<sup>25</sup>, inhibits IL-12 production<sup>26</sup> and promotes dendritic cell apoptosis and in the consequence suppresses T cell activation<sup>27</sup>. Moreover, 1,25(OH)<sub>2</sub>D<sub>3</sub> has direct effect on CD4<sup>+</sup> Th differentiation leading to reduction of Th17 and Th1 cells, which play a crucial role in a chronic inflammation by driving the inflammatory response through cytokine release.<sup>28</sup> Unsurprisingly, exposure to 1,25(OH)<sub>2</sub>D<sub>3</sub> reduces the expression of Th1-associated cytokines (IL-2, TNF- $\alpha$ , and Interferon  $\gamma$ - IFN $\gamma$ ) as well as those linked to Th17 (IL-17A, IL-17F, IL-21, IL-22).<sup>29</sup> On the other hand, vitamin D<sub>3</sub> enhances the immunomodulating responses of Th2 cells<sup>30,31,32</sup> increasing expression of IL-4 and IL-5<sup>33</sup>. It also inhibits the proliferation of activated B cells, promotes their apoptosis, and prevents plasma cell differentiation and immunoglobulin secretion<sup>34</sup>. Therefore, vitamin D deficiency could contribute to the development of B cell-mediated autoimmune disorders.<sup>35</sup> Conversely, vitamin D supplementation may have positive effects on B cell-mediated autoimmune diseases like SLE and RA.

Animal models suggest that 1,25(OH)<sub>2</sub>D can prevent and treat experimental arthritis<sup>36,37</sup>. Zhou et al. showed that mice with collagen-induced arthritis, which were administered 1,25(OH)<sub>2</sub>D<sub>3</sub> intraperitoneally, experienced a shift in CD4<sup>+</sup> differentiation from a Th1-Th17 phenotype to a more favorable Treg phenotype. This treatment was associated with a lower incidence and reduced clinical severity of arthritis, as well as a diminished erosive burden.<sup>38</sup>

Human studies examining the relationship between serum vitamin D concentrations and RA disease activity have shown mixed results. Although it remains uncertain if RA patients are more susceptible to vitamin D deficiency, there is strong evidence showing an inverse relationship between vitamin D levels and disease activity once RA is present<sup>39</sup>. Moreover, data from the Iowa Women's Health Study (IWHS) indicate that higher vitamin D intake might offer a protective effect against the onset of RA.<sup>40</sup> Nonetheless, vitamin D is known to

have local effects within inflamed joints and is often prescribed to RA patients for osteoporosis treatment or prevention<sup>41</sup>.

Li et al. (2018)<sup>42</sup> conducted a study in which they compared the effects of a placebo, 22-oxa-calcitriol at a dose of 50,000 IU/week, and calcitriol at the same dose on the treatment of rheumatoid arthritis. Both 22-oxa-calcitriol and calcitriol successfully decreased swollen joints in patients with rheumatoid arthritis ( $p < 0.0001$ ,  $q = 5.82$ ) and ( $p < 0.0001$ ,  $q = 5.82$ ), and both improved Health Assessment Questionnaire Disease Activity Index scores. Significant improvement in the number of swollen joints was observed for both 22-oxa-calcitriol and calcitriol – ( $p < 0.0001$ ,  $q = 5.82$ ) and ( $p < 0.0001$ ,  $q = 5.82$ ), respectively. Similarly, a reduction in pain was observed compared to the placebo ( $6.12 \pm 0.59$  vs.  $5.15 \pm 0.81$ ,  $p = 0.005$ ,  $q = 4.07$ ), ( $5.82 \pm 0.62$  vs.  $5.04 \pm 0.51$ ,  $p = 0.018$ ,  $q = 3.43$ ).

Sourier et al. (2019)<sup>43</sup> in a prospective randomized placebo-controlled trial involving 59 RA patients, who were either given vitamin D 100,000IU or a placebo. evaluated the short-term efficacy of vitamin D (cholecalciferol) supplementation on functional disability in RA patients with vitamin D deficits. Results showed a slight improvement in HAQ scores for the vitamin D group compared to the placebo group ( $+0.08 \pm 0.25$ ), and ( $-0.03 \pm 0.23$ ) ( $p = 0.11$ ) respectively. After adjusting for age, gender, season, and initial vitamin D serum level, the between-group difference achieved statistical significance (  $-0.03 \pm 0.23$  vs.  $0.08 \pm 0.25$ ,  $p = 0.046$ ). However there was no differences observed in the VAS pain, VAS activity, VAS fatigue, RAID nor SF-36 scores.

Giovani et al. (2019)<sup>44</sup> examined the effects of vitamin D supplementation in patients with and without vitamin D deficiency. The overall mean VAS pain decreased from 5.8 to  $4.8 \pm 2.3$ , which was not statistically significant. However, in patients with baseline vitamin D deficiency, VAS pain significantly decreased from  $6.8 \pm 1.9$  to  $5.4 \pm 2.0$  ( $p < 0.01$ ). For DAS28-CRP, there was a general trend towards a decrease to  $3.2 \pm 1.2$  at 3 months, but this was not statistically significant overall. In patients with sufficient baseline vitamin D levels ( $\geq 20$  ng/mL), DAS28-CRP significantly decreased from  $3.7 \pm 0.7$  to  $2.9 \pm 1.0$ . These findings suggest that vitamin D may have different effects on disease activity and pain in patients with rheumatoid arthritis (RA), depending on baseline serum levels of 25OHD.

According to RCT conducted by Alotaibi et al. (2021)<sup>45</sup> there is a significant negative correlation between DAS-28 with serum vitamin D3 ( $r = 0.437$ ,  $p = 0.001$ ). Improvement of vascular function indicated by enhanced flow-mediated dilatation (FMD), ( $r = 0.315$ ,  $p = 0.002$ ) and vitamin D serum level were correlated as well. This improvement is likely due to the regulation of adhesion molecules and inflammatory mediators.<sup>46</sup>

These findings collectively suggest that while vitamin D supplementation may not uniformly affect all RA patients, it can provide substantial benefits in terms of reducing disease activity, pain, and methotrexate-related side effects, particularly in those with baseline vitamin D deficiency or lower serum vitamin D levels. Thus, vitamin D supplementation represents a valuable adjunctive therapy in the management of RA. However, it should be noted that the studies are conducted on small groups and are very heterogeneous. The results of preclinical studies do not seem to be as conclusive as the results of studies on animal models and in vitro.

## **Vitamin E**

Vitamin E, a significant fat-soluble antioxidant, might help manage proliferative and destructive synovitis in RA by addressing the role of oxygen free radicals in the disease.<sup>47</sup> Through the action of tocopherol, vitamin E can potentially restore normal levels of reactive oxygen species scavengers and regulate eicosanoic acid production.

The murine studies investigated the effects of  $\gamma$ -tocotrienol,  $\delta$ -tocotrienol, and palm tocotrienol on rats with RA induced by intradermal injection of a collagen-complete Freund's adjuvant mixture. These rats were treated with tocotrienols after joint inflammation onset, significantly reducing paw edema, degenerative joint changes and inflammatory marker levels.<sup>48,49,50</sup>

Another study focused on the impact of tocotrienol on fibroblast-like synoviocytes (FLS) from RA patients, Th17 cell differentiation, and osteoclastogenesis in peripheral blood mononuclear cells (PBMCs). Tocotrienol inhibited Th17 formation, RANKL production, and TNF- $\alpha$  expression in FLS, likely through the suppression of mTOR, ERK, and I $\kappa$ B $\alpha$  pathways, and enhancement of AMPK phosphorylation. Additionally, tocotrienol reduced osteoclastogenesis markers, suggesting its potential in preventing bone resorption in RA<sup>51</sup>

Nguyen et al. (2021) included two RCTs in meta-analysis in order to assess the efficacy of vitamin E supplementation in reduction of the pain in patients suffering from RA. On 85 patients in two groups, the mean difference (95% CI) in VAS pain was -0.47 (-1.67; 0.74) cm ( $p = 0.45$ ), thus not statistically significant.<sup>52</sup> There was a high heterogeneity in the studies ( $I^2 = 80\%$ ). The authors concluded that effect of vitamin E supplementation for treatment RA is limited.

In the contrast, in 2022 Haiyang et al. conducted a systematic review with meta-analysis, which ultimately included nine publications involving a total of 39,845 patients. Vitamin E supplementation was found to be effective in individuals with RA for reducing tender joints

(MD = -1.66, 95%CI = -6.32; 2.99, I<sup>2</sup> = 93%, p < 0.00001) and swollen joints (MD = -0.46, 95%CI = -1.98;1.07, I<sup>2</sup> = 56%, p = 0.08).<sup>53</sup>

Even though evidence based on large population points to the benefits of vitamin E in managing RA symptoms, further research with more consistent methodologies is needed to clarify its role definitively.

### **Vitamin C**

Vitamin C, or ascorbic acid, is recognized as a highly effective antioxidant<sup>54</sup>. Animal studies have demonstrated positive effects of vitamin C supplementation in treating rheumatoid arthritis<sup>55</sup>. In RA patients, the breakdown of vitamin C by gut microbiota has been linked to increased levels of the pro-inflammatory cytokines TNF- $\alpha$  and IL-6. This indicates that gut microbiota might contribute to RA progression by facilitating vitamin C degradation.<sup>56</sup> Nevertheless, there is currently no evidence supporting the use of vitamin C supplementation to rebalance gut microbiota and prevent RA exacerbation through the gut-joint axis.

### **Vitamin K**

Several studies have demonstrated that vitamin K can inhibit NF- $\kappa$ B expression, leading to reduced inflammation<sup>57,58</sup>. Beyond its anti-inflammatory properties, vitamin K is also essential for the gamma-carboxylation of certain proteins involved in blood clotting and bone metabolism<sup>59,60</sup> but also acts as an antioxidant<sup>61</sup>. It was also suggested that women with RA might gain advantages from using vitamin K as an adjunct therapy<sup>62</sup>.

A study by Shishavan et al. involving 64 patients evaluated the effectiveness of vitamin K supplementation in treating rheumatoid arthritis (RA). The research primarily concentrated on a biomarker associated with joint damage (serum levels of matrix metalloproteinase-3), noting that data on clinical activity (DAS-28) were sparse. The DAS-28 score appeared to reduce in the vitamin K group (-12.56%, p = 0.041) compared to the baseline. However, this reduction was not statistically significant when compared to the placebo group.<sup>63</sup>

Taking that into consideration use of vitamin K in the treatment of rheumatoid arthritis seems to be limited.

### **Folic acid**

Methotrexate is a drug of the first choice in the treatment of rheumatoid arthritis and is integral to most combination therapies for the patients with rheumatoid arthritis.<sup>64</sup> Folic acid is prescribed alongside methotrexate, because its supplementation is linked to methotrexate's



role as a folate antagonist, aiming to mitigate adverse effects caused by folate deficiency<sup>65</sup>. Folic acid supplementation can reduce MTX-related side effects, especially liver function abnormalities<sup>66</sup>.

Stamp et al. evaluated two different doses of folic acid (5 mg and 0.8 mg per week) in 40 patients with active RA, defined by a DAS-28 score of 3.2 or higher. After 6 months, they found no significant difference in the change in DAS-28 between the two doses:  $-0.13$ ; 95% CI ( $-0.69$ ;  $0.43$ ) for the 5 mg group compared to  $-0.25$ ; 95% CI ( $-0.87$ ;  $0.37$ ) for the 0.8 mg group;  $p = 0.78$ . Additionally, there was no significant difference in methotrexate-related side effects between the two groups.<sup>67</sup>

In a separate trial, Morgan et al. investigated the impact of two weekly doses of folic acid (5 mg or 27.5 mg) versus a placebo on the efficacy and toxicity of methotrexate therapy in 94 patients. They found that folic acid supplementation, at either dose, did not influence the effectiveness of methotrexate as measured by joint tenderness, swelling indices, and the HAQ score. However, those receiving folic acid had significantly lower toxicity scores compared to the placebo group ( $p < 0.001$ ), with no notable difference between the two folic acid regimens.<sup>68</sup>

In conclusion, both studies underscore that varying doses of folic acid supplementation do not significantly alter the efficacy of methotrexate therapy in patients with active RA, as evidenced by changes in DAS-28 scores, joint tenderness, and swelling indices. However, folic acid supplementation plays a crucial role in reducing methotrexate-related toxicity.

Therefore, while the efficacy of methotrexate remains consistent regardless of folic acid dose, the inclusion of folic acid as a supplement is beneficial for minimizing adverse effects, supporting its use as an adjunct therapy in RA treatment regimens<sup>69</sup>.

## **Selenium**

Selenium is recognized for its crucial role in protecting cells from oxidative damage by influencing the levels and activities of antioxidant selenoenzymes – GPx-GPx1, GPx4, GPx3, GPx6, and GPx5.<sup>70,71</sup> Selenium also exerts anti-inflammatory functions by inhibiting the NF- $\kappa$ B cascade and reducing the production of inflammatory mediators.<sup>72,73</sup>

Zamani et al. evaluated in the randomized double-blind placebo-controlled trial the effect of selenium supplementation on 59 patients with rheumatoid arthritis. Participants received 200  $\mu$ g/day of selenium or a placebo for 12 weeks. The study showed that selenium supplementation cause a small improvement in ESR [0.38, 95% CI ( $-0.14$ ;  $0.89$ )] and anti-CCP serum levels [0.32, 95% CI ( $-0.2$ ;  $0.83$ )]. The mean DAS.CRP and DAS.ESR scores

decreased significantly in both groups, but the comparisons between the groups did not show a significant difference.<sup>74</sup>

These findings suggest that while selenium supplementation may offer some benefits, its impact on RA disease activity requires further investigation.

## **Conclusion**

In conclusion, the influence of physical activity on serum inflammatory markers in RA patients appears to be limited, highlighting a significant gap in current knowledge and the need for further research. This underscores the importance of exploring complementary treatment strategies, such as oral vitamin supplementation. The findings suggest that while vitamin D supplementation may not benefit all RA patients uniformly, it can significantly reduce disease activity, alleviate pain, and mitigate methotrexate-related side effects, especially in those with baseline vitamin D deficiency or lower serum levels.

However, existing studies often involve small, heterogeneous groups, and preclinical results are less conclusive than those from animal models and in vitro studies. Although population studies suggest potential benefits of vitamin E in managing RA symptoms, further research with consistent methodologies is needed to definitively clarify its role. The use of vitamin K in RA treatment remains limited, and there is no evidence supporting vitamin C supplementation.

Moreover, while selenium supplementation may offer some benefits, its impact on RA disease activity requires further investigation. On the other hand, folic acid supplementation is beneficial in minimizing the adverse effects of methotrexate, supporting its use as an adjunct therapy in RA treatment regimens. These findings underscore the need for continued research to optimize the role of various vitamins in managing rheumatoid arthritis effectively.

Nonetheless, the potential anti-inflammatory and antioxidative properties of certain vitamins suggest that they may play a supportive role in RA treatment. Further well-designed RCTs and meta-analyses are necessary to establish definitive conclusions and optimal supplementation protocols.

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The authors report no conflict of interest.

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