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General Medicine

VITAMIN D DEFICIENCY AND ITS ASSOCIATION WITH DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS

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ABSTRACT

"Rheumatoid arthritis (RA)" is a chronic autoimmune disease characterized by joint inflammation, synovial hyperplasia, and systemic manifestations. Emerging evidence highlights the role of vitamin D not only in bone metabolism but also as an immunomodulator influencing disease activity in RA. This review explores the multifactorial relationship between vitamin D deficiency and RA, focusing on immune pathways, epidemiological trends, disease activity indices, comorbidities, and therapeutic outcomes. Vitamin D modulates key inflammatory responses by affecting T-cell differentiation and cytokine production, thereby influencing the course of RA. Deficiency is highly prevalent among RA patients and correlates with higher disease activity scores, increased joint damage, and reduced bone mineral density. Supplementation has shown promise in reducing disease severity and improving fatigue and comorbid outcomes, although results remain variable across populations. Genetic polymorphisms and epigenetic changes in vitamin D pathway genes may partly explain this variability. Despite ongoing debate, vitamin D assessment and correction represent a low-risk, potentially beneficial adjunct to conventional RA therapies. Future research should aim at optimizing supplementation strategies based on individual patient profiles. The findings underscore the clinical importance of addressing vitamin D status in RA management to improve outcomes and reduce the burden of disease.

1. INTRODUCTION

"Rheumatoid arthritis (RA)" is a chronic, systemic autoimmune disease defined by persistent synovitis, progressive joint destruction, and extra-articular manifestations. Affecting nearly 1% of the world population, RA imposes significant personal, societal, and economic burdens due to its long-term disability and treatment costs [1]. Although its precise etiology remains elusive, it is widely accepted that a combination of genetic predisposition, environmental triggers, and immune dysregulation contribute to disease onset and progression.

Vitamin D, that maintains the calcium homeostasis and bone metabolism, has emerged as a potential immunomodulator. Its active form, calcitriol (1,25-dihydroxyvitamin D), influences both innate and adaptive immune outcomes, including the suppression of pro-inflammatory cytokines and modulation of T-helper cell activity [2]. These immunological effects have generated considerable interest in the potential role of vitamin D deficiency in autoimmune conditions, particularly RA.

Multiple observational studies suggest a high figure of vitamin D deficiency among RA patients, leading to speculation about its role not only in disease susceptibility but also in activity and prognosis [3]. Moreover, the expression of "vitamin D receptors (VDRs)" on synovial and immune cells highlights a plausible link between vitamin D signaling and joint inflammation.

Understanding this association could provide insights into non-pharmacological strategies to complement conventional "disease-modifying antirheumatic drugs (DMARDs)". This review aims to explore current evidence on the relation between vitamin D status and disease activity in RA, critically examining biological mechanisms, epidemiological trends, clinical outcomes, and therapeutic implications in light of recent studies.

2. Pathophysiology of RA and Vitamin D's Immuno-modulatory Role

RA arises from a complex interplay of immune dysfunction, genetic susceptibility, and environmental factors, culminating in chronic synovial inflammation. Central to its pathogenesis is the activation of antigen-presenting cells and T-helper (Th) cells, particularly Th1 and Th17 subtypes, which drive pro-inflammatory cascades. Cytokines such as "tumor necrosis factor-alpha (TNF-α)", "interleukin-1 (IL-1)", and "interleukin-6 (IL-6)" are overexpressed, contributing to synovial proliferation, cartilage degradation, and bone erosion [4].

Vitamin D, through its active form calcitriol, exerts widespread immunomodulatory effects. The VDR, expressed on dendritic cells, macrophages, and T and B lymphocytes, facilitates these effects by modulating gene transcription involved in inflammation [5]. Notably, vitamin D suppresses the expression of IL-2 and interferon-gamma, while enhancing the development of "regulatory T cells (Tregs)", thereby promoting immune tolerance [6]. In RA, these actions may mitigate autoimmune responses and tissue damage.

In addition, vitamin D inhibits antigen-presenting cell maturation and reduces the differentiation of Th17 cells, which are implicated in RA-associated synovitis and osteoclastogenesis. These mechanisms suggest a potentially protective role against disease initiation and progression. Experimental studies have also demonstrated that vitamin D analogs can downregulate matrix metalloproteinases involved in cartilage breakdown, further supporting its role in preserving joint integrity [7].

3. Epidemiology of Vitamin D Deficiency in RA Patients

Vitamin D deficiency is a widespread public health concern, particularly among individuals with chronic inflammatory diseases such as RA. Epidemiological studies consistently demonstrate a higher prevalence of hypovitaminosis D in RA patients compared to the general population [8]. This deficiency is especially pronounced in certain geographical areas where sunlight exposure is limited or seasonal, and in populations with darker skin pigmentation or cultural practices limiting skin exposure to sunlight.

Data from multiple cohort studies reveal that between 40% to 80% of RA patients exhibit serum 25-hydroxyvitamin D levels below the recommended threshold of 30 ng/mL [9]. Factors contributing to this include limited outdoor activity due to joint pain or disability, use of corticosteroids which interfere with vitamin D metabolism, and comorbid conditions such as obesity or gastrointestinal malabsorption syndromes [10].

In the Indian subcontinent and parts of the Middle East,

despite abundant sunlight, vitamin D deficiency in RA patients remains highly prevalent, attributed to low dietary intake, indoor lifestyles, and cultural dress norms [11]. A recent cross-sectional study from Eastern India reported that nearly 70% of RA patients had suboptimal vitamin D levels, with a significant correlation to disease activity indices [12].

4.Vitamin D Status and RA Disease Activity Measures

Numerous clinical investigations have explored the association between serum vitamin D levels and disease activity in RA, with compelling evidence pointing to an inverse relationship. Disease activity in RA is commonly measured using validated tools such as the "Disease Activity Score in 28 joints (DAS28)", "Visual Analog Scale for pain (VAS)", "erythrocyte sedimentation rate (ESR)", and "C-reactive protein (CRP)" levels. Patients with lower vitamin D concentrations often demonstrate higher DAS28 and VAS scores, suggesting more active disease [13].

One large observational study indicated that patients with vitamin D levels below 20 ng/mL were significantly more likely to present with moderate to severe disease activity compared to those with sufficient levels [14]. This trend held true across different age groups and durations of disease, indicating a consistent relationship between deficiency and inflammatory burden. Furthermore, patients with adequate vitamin D levels showed better control of symptoms and lower levels of systemic inflammation.

Some evidence also supports a dose-response effect. Incremental increases in serum vitamin D have been linked with proportional reductions in disease activity markers, implying that even modest supplementation may yield clinical benefits [15]. However, not all studies uniformly confirm this association. Inconsistencies in findings may be due to confounders such as seasonal variation, differing thresholds for deficiency, and concurrent medications.

5. Impact on Joint Damage and Bone Metabolism

RA is not only a disease of synovial inflammation but also a significant contributor to progressive joint destruction and systemic bone loss. Chronic inflammation in RA accelerates osteoclast-mediated bone resorption, leading to juxta-articular osteoporosis and erosions. Vitamin D plays a pivotal role in bone metabolism, and its deficiency may aggravate structural joint damage and decrease "bone mineral density (BMD)" in RA patients [16].

Vitamin D promotes calcium absorption and regulates parathyroid hormone (PTH) levels, both of which are critical for maintaining skeletal integrity. In RA, persistent inflammation further disrupts this balance by increasing "receptor activator of nuclear factor kappa-B ligand (RANKL)" expression and decreasing "osteoprotegerin (OPG)", tipping the scale toward osteoclast activation. Vitamin D has been shown to modulate this axis by downregulating RANKL and promoting OPG expression, thereby reducing osteoclastic activity [17].

Clinical studies have documented a higher prevalence of generalized and localized osteoporosis in RA patients with low vitamin D status. This bone loss is exacerbated by glucocorticoid therapy, physical inactivity, and chronic systemic inflammation. Furthermore, RA patients with vitamin D deficiency may experience delayed bone healing and poorer outcomes following joint replacement surgeries [18].

6. Influence of Vitamin D on Comorbidities in RA

RA is often accompanied by a spectrum of systemic comorbidities that complicate disease management and worsen long-term outcomes. Vitamin D deficiency, frequently observed in RA patients, is implicated not only in joint inflammation but also in the development and exacerbation of common RA-related comorbidities including cardiovascular disease, metabolic syndrome, fatigue, and periodontal disease [19].

Cardiovascular complications, a leading cause of mortality in RA, are closely linked to chronic systemic inflammation. Vitamin D plays a role in endothelial function and inhibits vascular smooth muscle proliferation. Deficiency has been associated with elevated levels of pro-inflammatory cytokines such as IL-6 and TNF-α, which are known contributors to atherosclerosis and increased arterial stiffness. RA patients with low vitamin D levels show higher prevalence of hypertension, dyslipidemia, and carotid intima-media thickness, all markers of cardiovascular risk [20].

Fatigue, a commonly reported but often under-addressed symptom in RA, has also been linked to suboptimal vitamin D status. Some studies suggest that repletion of vitamin D improves fatigue scores independently of joint disease activity, highlighting its systemic role in energy metabolism and muscle function.

Moreover, vitamin D influences periodontal health, which is relevant given the established association between periodontitis and RA. Both conditions share inflammatory pathways, and deficiency in vitamin D may contribute to poor oral health in RA patients.

7.Vitamin D Supplementation in RA: Clinical Outcomes

The potential therapeutic benefit of vitamin D supplementation in RA has garnered growing interest, especially given its immunomodulatory properties and ease of administration. Clinical trials and observational studies have attempted to evaluate whether correcting vitamin D deficiency can reduce disease activity, improve quality of life, or prevent structural joint damage in RA patients [20].

Evidence from interventional studies suggests that vitamin D supplementation, when administered to deficient individuals, can modestly reduce RA disease activity scores, including DAS28 and VAS for pain. One randomized trial reported that patients receiving cholecalciferol (vitamin D_3) in addition to standard DMARDs experienced a greater reduction in joint swelling and tenderness compared to those receiving DMARDs alone. These effects, however, appeared to be more pronounced in patients with severe baseline deficiency and early disease duration.

Dosage regimens vary widely, ranging from daily low doses (800–2000 IU) to high intermittent doses (50,000 IU weekly). Most studies agree that supplementation is safe and well-tolerated, with minimal adverse effects, although the optimal dose for immunologic benefits remains unclear.

Despite these encouraging findings, not all studies show consistent improvements in clinical outcomes, and some fail to find a statistically significant difference. This may be due to variations in patient populations, supplementation protocols, and confounding variables such as sun exposure, BMI, or concurrent medications.

8. Molecular and Genetic Interactions

Beyond its role in calcium regulation and immune modulation, vitamin D exerts profound effects at the molecular and genetic levels, which are particularly relevant in the context of RA. The biological activity of vitamin D is mediated through binding to the "vitamin D receptor (VDR)", a nuclear transcription factor expressed in numerous immune and synovial cells. This receptor-VDR complex regulates the expression of over 200 genes, many of which are involved in inflammatory and autoimmune processes [13].

Polymorphisms in the VDR gene have been linked to RA susceptibility and disease severity. Certain variants may reduce the receptor's binding efficiency or alter downstream

gene activation, thereby impairing the anti-inflammatory response of vitamin D. For instance, studies have identified that individuals with specific VDR genotypes exhibit higher RA disease activity and greater radiographic progression compared to those with wild-type alleles [14].

Additionally, recent research highlights epigenetic modifications in vitamin D pathway genes, such as altered methylation patterns in "CYP27B1 (encoding 1-α hydroxylase)" and "CYP24A1 (encoding 24-hydroxylase)", which influence local synthesis and degradation of active vitamin D in inflamed synovial tissue [15]. These modifications may explain the variability in treatment response and underscore the need for individualized vitamin D therapy.

Understanding these molecular and genetic interactions helps clarify why some RA patients remain unresponsive to supplementation despite biochemical correction of deficiency. Future therapeutic approaches may involve genotyping or personalized dosing strategies to optimize the immunoregulatory effects of vitamin D in RA.

CONCLUSION

Vitamin D plays a multifaceted role in RA, influencing immune regulation, disease activity, bone health, and associated comorbidities. While numerous studies support an inverse relationship between vitamin D levels and RA severity, inconsistencies persist due to genetic variability, environmental factors, and methodological differences. Despite these limitations, routine screening and correction of vitamin D deficiency in RA patients appear justified given its potential benefits and safety. Personalized approaches, including genetic and epigenetic profiling, may further enhance therapeutic outcomes. Overall, vitamin D remains a valuable adjunct in the comprehensive management of RA, warranting continued investigation through well-designed clinical trials.

REFERENCES

1. Miler, M., Nikolac Gabaj, N., Grazio, S., Vahtaric, A., Vrtaric, A., Grubišic, F., ... Vrki , N. (2020). Lower concentration of vitamin D is associated with lower DAS28 and VAS-pain scores in patients with inflammatory rheumatic diseases treated with infliximab: A pilot study. Rheumatology International, 40(9), 1455–1461. https://doi.org/10.1007/s00296-020-04607-3
2. Tv, P., Kumar, B., Chidambaram, Y., & Thangavelu, S. (2023). Correlation of rheumatoid arthritis disease severity with serum vitamin D levels. Clinical Nutrition ESPEN, 57, 697–702. https://doi.org/10.1016/j.clnesp.2023.08.025
3. Mouterde, G., Gamon, E., Rincheval, N., Lukas, C., Seror, R., Berenbaum, F., ... Combe, B. (2020). Association between vitamin D deficiency and disease activity, disability, and radiographic progression in early rheumatoid arthritis: The ESPOIR cohort. The Journal of Rheumatology, 47(11), 1624–1628. https://doi.org/10.3899/jrheum.190795
4. Alharbi, S., Alharbi, R., Alhabib, E., Ghunaim, R., & Alreefi, M. M. (2023). Vitamin D deficiency in Saudi patients with rheumatoid arthritis. Cureus, 15(2), e34815. https://doi.org/10.7759/cureus.34815
5. Zou, J., Zhu, L., Yang, J., Feng, J., Li, S., Luo, J., ... Tian, L. (2022). Correlation between vitamin D metabolites and rheumatoid arthritis with osteoporosis by ultra-high-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). Journal of Bone and Mineral Metabolism, 40(4), 696–703. https://doi.org/10.1007/s00774-022-01337-3
6. Choudhury, C., Sahib, A., Karmakar, P., & Kar, S. (2024). Correlation of serum vitamin D and high-density lipoprotein (HDL) cholesterol levels with disease activity in rheumatoid arthritis: A single-center experience from Eastern India. Cureus, 16(9), e69333. https://doi.org/10.7759/cureus.69333
7. Du, L. Y., Zhang, M. J., Liu, P. F., Xiao, G., & Lyu, X. M. (2021). [Correlation between serum CCL20 level and disease severity in patients with rheumatoid arthritis]. Zhonghua Yu Fang Yi Xue Za Zhi, 55(2), 226–232. https://doi.org/10.3760/cma.j.cn112150-20200917-01209
8. Harrison, S. R., Jutley, G., Li, D., Sahbudin, I., Filer, A., Hewison, M., & Raza, K. (2020). Vitamin D and early rheumatoid arthritis. BMC Rheumatology, 4, 38. https://doi.org/10.1186/s41927-020-00134-7
9. Dobrovolskaya, O. V., Toroptsova, N. V., Nikitinskaya, O. A., Samarkina, E. Y., Cherkasova, M. V., & Feklistov, A. Y. (2021). [Vitamin D status in women with rheumatoid arthritis: Frequency of hypovitaminosis, associations with disease activity, body composition and comorbidity]. Terapevticheskii Arkhiv, 93(5), 581–586. https://doi.org/10.26442/00403660.2021.05.200790
10. Elfituri, S. (2024). The effects of vitamin D supplementation on disease activity and fatigue in Libyan rheumatoid arthritis patients. Reumatologia, 62(2), 109–114. https://doi.org/10.5114/reum/187391
11. Ravikanth, R., & Singh, J. K. (2020). Semi-quantitative analysis of 18F fluorodeoxyglucose uptake in the assessment of disease activity and therapeutic response in rheumatoid arthritis: An institutional experience. World Journal of Nuclear Medicine, 19(4), 347–352. https://doi.org/10.4103/wjnm.WJNM_12_20
12. Yong, W., Hongbin, L., Jing, W., Jing, Z., Ning, T., & Lijie, B. (2020). Associations of changes in serum inflammatory factors, MMP-3, 25(OH)D and intestinal flora with osteoporosis and disease activity in rheumatoid arthritis patients. Clinical Laboratory, 66(12). https://doi.org/10.7754/Clin.Lab.2020.200242
13. Punceviciene, E., Rovas, A., Puriene, A., Stuopelyte, K., Vitkus, D., Jarmalaite, S., & Butrimiene, I. (2021). Investigating the relationship between the severity of periodontitis and rheumatoid arthritis: A cross-sectional study. Clinical Rheumatology, 40(8), 3153–3160. https://doi.org/10.1007/s10067-021-05661-3
14. Rivera-Escoto, M., Campos-López, B., Pesqueda-Cendejas, K., Ruiz-Ballesteros, A. I., Mora-García, P. E., Meza-Meza, M. R., ... De la Cruz-Mosso, U. (2024). Analysis of potential vitamin D molecule biomarkers: Association of calcitriol and its hydroxylation efficiency ratio with cardiovascular disease risk in rheumatoid arthritis patients. Biomedicines, 12(2), 273. https://doi.org/10.3390/biomedicines12020273
15. Sukharani, N., Dev, K., Rahul, F., Bai, P., Ali, A., Avinash, F., ... Rizwan, A. (2021). Association between rheumatoid arthritis and serum vitamin D levels. Cureus, 13(9), e18255. https://doi.org/10.7759/cureus.18255
16. Guan, Y., Hao, Y., Guan, Y., Bu, H., & Wang, H. (2020). The effect of vitamin D supplementation on rheumatoid arthritis patients: A systematic review and meta-analysis. Frontiers in Medicine, 7, 596007. https://doi.org/10.3389/fmed.2020.596007
17. Punceviciene, E., Gaizevska, J., Sabaliauskaite, R., Šnipaitiene, K., Venceviciene, L., Vitkus, D., ... Butrimien , I. (2022). Analysis of epigenetic changes in vitamin D pathway genes in rheumatoid arthritis patients. Acta Medica Lituanica, 29(1), 78–90. https://doi.org/10.15388/Amed.2021.29.1.7
18. Clasen, J. L., Cole, R., Aune, D., Sellon, E., & Heath, A. K. (2023). Vitamin D status and risk of rheumatoid arthritis: Systematic review and meta-analysis. BMC Rheumatology, 7(1), 3. https://doi.org/10.1186/s41927-023-00325-y
19. Bose, D., Ravi, R., Maurya, M., Legha, R., & Konwar, M. (2023). Vitamin D deficiency in rheumatoid arthritis patients of India: A single-arm meta-analysis. African Health Sciences, 23(1), 795–806. https://doi.org/10.4314/ahs.v23i1.84
20. Cieslewicz, A., Korzeniowska, K., Grabanska-Martynska, K., Jablecka, A., & Hrycaj, P. (2024). Seasonal and treatment-related variation in 25-hydroxy vitamin D concentration in patients with rheumatoid arthritis. Journal of Clinical Medicine, 13(4), 973. https://doi.org/10.3390/jcm13040973