International Journal of Biomedicine 16(3) (2026) 314-319
http://dx.doi.org/10.21103/Article16(3)_RA3

REVIEW ARTICLE

INTERNATIONAL JOURNAL OF BIOMEDICINE

Rheumatoid Arthritis: Independent and Synergistic Effects of Vitamin D Deficiency and Smoking

Abdulsalam A. Noorwali

Department of Internal Medicine, Faculty of Medicine, Umm Al-Qura University, Makkah 21955, Saudi Arabia

Abstract

Rheumatoid arthritis (RA) is a long-term autoimmune disease in which the immune system mistakenly attacks the joint linings. The exact cause of RA is still not evident. However, a combination of environmental and genetic factors is considered to contribute to RA. Smoking is an established environmental condition/ risk that exacerbates the disease activity and severity, including faster joint damage, increased lung and other systemic complications, and decreased efficacy of medication used by RA patients. There are a number of factors that synergistically affect the health of smokers, RA patients, or smoking RA patients. Vitamin D (VitD) is one of the main factors involved in smoking and RA. Regarding synergistic influences and interactions, assessing inflammatory biomarker levels (e.g., high-sensitivity C-reactive protein [hs-CRP]) indicates that the inflammatory influence of VitD deficiency is significantly amplified and stronger in smokers than in non-smokers. Furthermore, smoking, a known environmental factor in interaction with the genetic factors, causes a synergistic risk of severe RA. Although both smoking and VitD are established risk factors for RA, the intricate details about how they influence independently are not clearly known. (International Journal of Biomedicine. 2026;16(3):314-319.)

Keywords: rheumatoid arthritis • smoking • vitamin D

For citation: Noorwali AA. Rheumatoid Arthritis: Independent and Synergistic Effects of Vitamin D Deficiency and Smoking. International Journal of Biomedicine. 2026;16(3):314-319. doi:10.21103/Article16(3)_RA3

Abbreviations

Anti-CCP, anti-cyclic citrullinated peptide; **CRP**, C-reactive protein; **CVDs**, cardiovascular diseases; **DAS28**, disease Activity Score 28; **DMARDs**, disease-modifying antirheumatic drugs; **ESR**, erythrocyte sedimentation rate; **hs-CRP**, high-sensitivity C-reactive protein; **MS**, multiple sclerosis; **25(OH)D**, 25-hydroxyvitamin D or vitamin D; **PMP-RA**, postmenopausal rheumatoid arthritis patients; **PTH**, parathyroid hormone; **RA**, rheumatoid arthritis; **RF**, rheumatoid factor; **Th1**, T lymphocyte helper 1; **Th7**, T lymphocyte helper 7; **VitD**, vitamin D; **VDR**, vitamin D receptor.

Introduction

Rheumatoid arthritis (RA) is a long-term autoimmune disease in which the immune system mistakenly attacks the joint linings.[1] Joints are primarily affected, presenting with swelling, stiffness, pain, and bone erosion. The wrist and hands are most commonly involved. Stiffness and pain often worsen after rest. Joints of both hands or both knees are affected symmetrically, and discomfort can spread to the lungs, heart, eyes, skin, blood, and nerves, leading to a range of complications.[2-4] The patients with RA may have a fever. Symptoms may take weeks to months to appear gradually.[1,5] The exact cause of RA is still not evident. However, a combination of environmental and genetic factors is considered to contribute to RA.[6] A comprehensive account of the cellular and molecular mechanisms, as well as effective therapies, for RA has been reviewed.[7]

Smoking is an established environmental condition/ risk that exacerbates the disease activity and severity, including faster joint damage, increased lung and other systemic complications, and decreased efficacy of medication used by RA patients8. Smoking can trigger the immune system in individuals with specific genes, leading to the production of antibodies such as anti-CCP (anti-cyclic citrullinated peptide) and RF (rheumatoid factor).[8,9]

There are a number of factors that synergistically affect

***Corresponding author:** Abdulsalam A. Noorwali, MD. Department of Internal Medicine, Faculty of Medicine, Umm Al-Qura University, Makkah 21955, Saudi Arabia. E-mail: aanoorwali@uqu.edu.sa*

the health of smokers, RA patients, or smoking RA patients. However, Vitamin D (VitD) or serum 25-hydroxyvitamin D [25(OH)D] is one of the main factors involved in smoking, RA, or smoking RA.[10] VitD levels in active smokers are significantly lower compared to those of non-smoking individuals.[11] The cumulative effect of VitD deficiency and smoking on systemic inflammation is more severe in smoking RA patients than in non-smoking RA patients, which makes it more difficult to manage.[12] Similarly, VitD and smoking synergistically influence disease activity, severity, and exacerbation of symptoms in RA patients.[13-16] To have insight into the independent effect of smoking on RA, the effect of VitD on smoking, and VitD on RA, as well as the cumulative or synergistic effect of smoking and VitD on RA, the present review was planned to be carried out.

Vitamin D in Healthy Individuals and Smokers

For general health, 600-800 international units (IUs) daily dosages of VitD are recommended generally, whereas deficiency conditions require 1000-2000 IUs daily, and severe deficiency conditions require 50,000 IUs weekly dosages. Deficiency levels <20 ng/mL (<50 nmol/L) indicate poor bone health (severe deficiency < 10 ng/mL may cause osteomalacia in adults and rickets in children). Sufficient levels>30 ng/mL (>75 nmol/L) are required for bone/ overall health. The insufficient levels of 20–30 ng/mL (52-72 nmol/L) or the sub-optimal levels require the administration/ supplementation of VitD to sufficient levels (> 30 ng/mL). VitD levels of above 150 ng/mL (375 nmol/L) cause toxicity and hypercalcemia. [17-19]

Main factors influencing the serum VitD levels are the extent of exposure to sun, age (older people have higher risk of VitD deficiency), skin pigmentation (less VitD production by darker skin via sun exposure), and malabsorption disorders.[20,21] Table-1 shows the VitD levels, status and cinical implications, explaining the outcomes in the statuses of sufficient or desirable, optimal, insufficient, and deficient levels and toxicity.

It is usually overlooked, but smoking is one of the main causes of the VitD deficiency.[11] Low VitD levels and VitD deficiency have been noted to increase impairment of the body's defense/immune system, especially lung damage.[4,22] Success in smoking cessation/quitting was obtained more in patients with high VitD levels.[23] It was found that there is a direct association of a decrease in VitD level with the number of cigarettes smoked as well as the duration of smoking habit.[24]

Deficient levels of VitD, causing increased levels of oxidative stress due to smoking, can increase the pulmonary conditions and the risks of having cancer, and its higher and beneficial levels are immunomodulatory and anti-inflammatory.[4] In smokers with sufficient VitD levels, lung function decreases more slowly over time than in those with insufficient VitD levels.[22]

VitD deficiency in second-hand or passive smoking occurs independently in adults and young children.[25,26] Both active and passive smokers may have a high risk of VitD deficiency, which can disrupt the VitD metabolism since exposure to smoking interferes with the process of VitD synthesis in the body.[11,26,27]

Smoking can alter the gene expression and VitD receptor (VDR) genes. It downregulates VitD receptors in the lungs, leading to a decline in circulating VitD.[28,29] VitD is necessary for calcium uptake. VitD-parathyroid hormone (PTH) axis and calcium absorption in the intestine are disrupted, leading to bone-related complications, e.g., osteoporosis, and bone loss due to cigarette smoking. Such effects occur due to the

Table 1.

Vitamin D levels, status, and clinical implications

Status	VitD serum levels	Risks/clinical implications/outcomes
Sufficient/ Desirable	≥ 30 ng/mL (≥75 nmol/L)	Reduction in the fall/fractures, sufficient for normal bone health and immune functions. Minimizes parathyroid hormone (PTH), increases calcium absorption and neuromuscular performance/activities.
Optimal	30-50 ng/mL (75-125 nmol/L)	Although 30 ng/mL is sufficient, 30-60 ng/mL is considered safe for general health. The levels of higher than 40 ng/mL improve immunity and reduce the risk of cardiovascular diseases (CVDs), multiple sclerosis (MS), and certain types of cancers.
Insufficient	21-29 ng/mL (50-75 nmol/L)	Insufficient or suboptimal levels associated with decreased calcium absorption may lead to lower bone density and secondary hyperparathyroidism.
Deficient	< 20 ng/mL (< 50 nmol/L)	Severe deficiency could be the risk for osteomalacia and rickets, respectively, in adults and children. Risks of falls/fractures, bone loss, weakness of proximal muscles, and chronic pain occur.
Toxicity	>100 ng/mL (>250 nmol/L)	Hypercalcemia, kidney damage, and related disorders occur.

Table 2.

Influence of smoking on VitD levels

Findings	Descriptions	Study Sources
Dose dependance	Vitamin D correlates inversely with the number of cigarettes smoked/ day	11,24
Decreased VitD levels	Smokers present lower VitD levels than non-smokers.	11
Increased risk of VitD deficiency	Daily smoking is associated with high vitamin D deficiency.	11,24
Cessation/ quitting smoking	High vitD levels are associated with high success rates for cessation/ quitting smoking.	23
Mechanisms	Smoking influences calcium levels, increases bone loss, and change gene expression	11,30

combined effect of nicotine and low levels of VitD.[30]

Smoking influences the sensitive association between VitD and parathyroid hormone and increases the bone mineral density, leading to the risk of osteoporosis.[30]

Thousands of toxic components of smoke can influence the endocrine system.[11,26] Liver and kidneys are involved in converting VitD to the usable active form. Smoking toxins change the expression of required enzymes and break the VitD before it can be used in the body.[11,26,27] Furthermore, cigarette smoking exacerbates chronic rhinosinusitis.[31]

Table 2 presents the influence of smoking on VitD levels, including dose dependence, decreased VitD levels, increased risk of VitD deficiency, cessation/ quitting of smoking, and the mechanisms whereby smoking influences VitD levels.

Vitamin D in Rheumatoid Arthritis

Vitamin D, or serum 25-hydroxyvitamin D [25(OH) D] (VitD), is considered a useful biomarker for assessing disease activity in patients with RA.[32,33] Appropriate doses of VitD improve Disease Activity Score 28 (DAS28), C-reactive protein (CRP) levels, and visual analog scale (VAS) for subjectively rating pain or global health, from "no pain" to "worst pain," in RA.[34,35] VitD has been shown to be significantly lower in RA compared to healthy controls.[36] Adequate levels of VitD are important for maintaining adequate bone density in RA patients with elevated chronic inflammation and osteoporosis.[37]

Strong bones are built if the required level of VitD is present to absorb calcium. Patients with RA experience altered bone turnover and mineralization. Hence, the patients with RA are supplemented with the necessary VitD to prevent bone loss and weakness.[38]

Important representative information of VitD levels in patients with RA is presented in Table 3. Lower serum vitamin D (VitD) levels are commonly observed in patients with RA, though a large proportion of patients show VitD deficiency due to increased disease activity and elevated inflammation/ pain.[39,40]

VitD deficiency in 22.3% RA patients (<20 ng/mL) and insufficiency in 42.7 % (20-29 ng/mL) was investigated in Saudi patients.[41] Another study revealed that RA with high disease activity showed the lowest VitD levels (18.25±8.3 nmol/L), moderate activity (VitD: 35.13±15.2 nmol/L), and low disease activity (VitD: 38.05±7.3 nmol/L).[42] Rossini et al.[43] found VitD deficiency in 29% (42/145) postmenopausal RA (PMP-RA) patients. A meta-analysis study presented lower levels of VitD (mean difference: 16.52 nmol/L) in RA.[44] Table 3 describes the VitD levels in patients with rheumatoid arthritis.

Several other authors have suggested their views and research output on the impact of VitD in patients with RA.[10,45-48] The safe upper intake limit for correcting VitD deficiency is generally 1000-4000 IU per day, and higher doses (e.g., 50,000 IU weekly) are used to monitor RA, whereas the recommended dosage is 1000-2000 IU of VitD, though this depends on specific cases.[46,48] VitD Supplementation with disease-modifying antirheumatic drugs (DMARDs) reduces erythrocyte sedimentation rate and other inflammatory biomarkers. The prevalence of VitD deficiency in RA patients ranges from 30% to 63%.[45]

VitD decreases the proliferation activity of inflammation-related Th1 (T lymphocyte helper 1) and Th7 (T lymphocyte helper 7) cells and increases the regulatory T cells to manage autoimmune joint damage.[46] As concerns disease activity, decreased vitamin D levels are inversely associated with higher DAS28 (Disease Activity Score 28) and, hence, lower levels of VitD are correlated with more joint swelling and worse symptoms.[10]

Some of the important findings includes, a) the role of VitD in RA correlating inversely to the level or scores

Table 3.

Vitamin D levels in patients with rheumatoid arthritis

Study	Subjects	Important findings
39	RA & healthy controls	VitD deficiency in 84% of RA patients compared with 34% of control subjects.
41	Saudi RA patients	VitD deficiency in 22.3% of RA (<20 ng/mL) and insufficiency in 42.7% (20-29 ng/mL).
42	RA & healthy controls	RA with high disease activity showed the lowest VitD levels (18.25±8.3 nmol/L), VitD levels in RA with moderate (35.13±15.2 nmol/L) and low (38.05±7.3 nmol/L) disease activity.
43	PMP-RA	VitD deficiency in 29% (42/145) of RA patients.
44	Meta-analysis	Lower levels of VitD (mean difference: 16.52 nmol/L) in RA

PMP-RA: postmenopausal patients with rheumatoid arthritis

Table 4.

Independent and synergistic effects of VitD and smoking in patients with rheumatoid arthritis.

Factors	Independent and synergistic effects in RA	Clinical consequences
VitD deficiency	High prevalence of RA	High disease activity, low functional capability, heightened level of pain
Smoking	Higher risk factor	Lower efficacy of medication, heightened level of susceptibility, and worsening of the symptoms of RA.
VitD supplementation	Efficacious	Decrease in disease activity and pain, especially in the starting phase of RA.
VitD deficiency+smoking	Synergistic effects	Decreasing trend for VitD and rising trend in inflammation.

of disease activity and to some of the known inflammatory biomarkers e.g., C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR),[49] b): the prevalence studies showing deficiency of VitD (less than 30 ng/ml) in 84% of the RA patients whereas 34 % in control subjects,[39] though the mean VitD levels documented in RA are usually lower (21.05±10.02 and 18.09± 8.99 ng/ml),[39] c): the supplementation of 50,000 IU of VitD3 was found affective for decreasing fatigue, pain and the disease activity in patients with RA,[49] and d): the immunomodulatory effect of VitD for differentiation of T-cells and production of cytokines manifests the beneficial effect of VitD for autoimmune disorders.[36]

VitD acts as an immunomodulator, helping reduce systemic inflammation, joint stiffness, and the severity of RA symptoms.[48] Furthermore, VitD is involved in promoting the differentiation process for regulatory T-cells, which does not allow the immune system to attack the joints mistakenly.[50]

The Birmingham early inflammatory cohort did not find a clear correlation between VitD and RA diagnosis/ progression, and no significant decrease in pain or fatigue was observed.[10] Another study[34] documented a strong negative association between high levels of hypovitaminosis and RA disease activity in their clinical trial and found that VitD supplements significantly improved DAS28 scores.

Vitamin D, Smoking, and Rheumatoid Arthritis

The impact and availability of VitD are changed significantly by smoking in RA patients, and deficiency of VitD in such conditions leads to inflammatory risks and disease severity.[51,52] Remission becomes quite low when, besides low VitD, the RA patient is a smoker.[10] It is known that smoking and RA both disturb bone metabolism, e.g., a high risk of osteoporosis. Smoking itself disrupts the VitD regulation and parathyroid actions, and more severe dysregulations occur in patients with RA.[52] The synergistic effect of VitD and smoking occurs. The association between VitD and high CRP (C-reactive protein) levels is significantly stronger in smoking RA patients.[12]

As presented in Table 4, there are independent effects of VitD as well as smoking in patients with RA. However, interlinked and synergistic effects of VitD and smoking lead to worsening of the disease activity/ outcomes as smoking is an important environmental factor that triggers the RA disease activity, and the deficiency of VitD causes increased disease activity/ severity, amplified inflammation, and bone fractures, disruption of bone metabolism, and decreased calcium absorption.[10,13,39,46, 51, 53]

Conclusion

Quitting smoking is a lifestyle intervention that is highly helpful, especially for someone with RA. It leads to improved bodily functions, reduced active symptoms, and greater treatment efficacy.[8] It is necessary to consult healthcare personnel for people who smoke to have their VitD level checked. The relevant consultant can determine the supplementation dose, taking into account respiratory risks and associated conditions.[22,23,26] It is essential to achieve the required level of VitD in patients with rheumatoid arthritis. The rheumatologist routinely recommends the VitD test. If VitD deficiency is confirmed, sunlight exposure, important dietary sources (e.g., fish [salmon, tuna, etc.], fortified foods, egg yolks), and supplementation with VitD are recommended.[33]

Correcting the VitD deficiency to >30 ng/mL helps decrease the DAS28 (Disease Activity Score) and improve the health of RA patients.[41] The condition of the patients with RA is assessed by the DAS28 clinical index, which measures the activity of RA by checking 28 important joints for their tenderness as well as swelling.[54]

Regarding synergistic influences and interactions, assessing inflammatory biomarker levels (e.g., high-sensitivity C-reactive protein [hs-CRP]) indicates that the inflammatory influence of VitD deficiency is significantly amplified and stronger in smokers than in non-smokers. Furthermore, smoking is a known environmental factor in interaction with genetic factors, causing a synergistic risk of severe RA. Although both smoking and VitD are established risk factors for RA, the intricate details about how they influence independently require further studies.

Sources of Funding

This research received no external funding.

Disclosure and Conflicts of Interest

The author declares that he has no conflicts of interest.

Disclaimer

The views expressed in the submitted article are those of the author and not those of the institution.

Author Contribution Statement

The author confirms sole responsibility for the conception, design, and writing of the manuscript.

References

1. Majithia V, Geraci SA. Rheumatoid arthritis: diagnosis and management. Am J Med. 2007 Nov;120(11):936-9. doi: 10.1016/j.amjmed.2007.04.005. PMID: 17976416.
2. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis. 2003 Aug;62(8):722-7. doi: 10.1136/ard.62.8.722. PMID: 12860726; PMCID: PMC1754626.
3. Cutolo M, Kitas GD, van Riel PL. Burden of disease in treated rheumatoid arthritis patients: going beyond the joint. Semin Arthritis Rheum. 2014 Feb;43(4):479-88. doi: 10.1016/j.semarthrit.2013.08.004. Epub 2013 Sep 27. PMID: 24080116.
4. Zeng H, Yuan Z, Wu RT, Huang Z. Research progress on complications of rheumatoid arthritis. Front Immunol. 2025 May 27;16:1561926. doi: 10.3389/fimmu.2025.1561926. PMID:

40496851; PMCID: PMC12149157.
5. Jahid M, Khan KU, Rehan-Ul-Haq, Ahmed RS. Overview of Rheumatoid Arthritis and Scientific Understanding of the Disease. Mediterr J Rheumatol. 2023 Aug 1;34(3):284-291. doi: 10.31138/mjr.20230801.oo. PMID: 37941854; PMCID: PMC10628871.
6. Masoumi M, Solaymani M, Abbasifard M, Houshmandfar S, Iravani P, Saeedi-Boroujeni A, Karami J. The genetic puzzle of rheumatoid arthritis: Causes, progression, and treatment. Biochem Biophys Rep. 2025 Jul 21;43:102148. doi: 10.1016/j.bbrep.2025.102148. PMID: 40734997; PMCID: PMC12305329.
7. Han P, Liu X, He J, Han L, Li J. Overview of mechanisms and novel therapies on rheumatoid arthritis from a cellular perspective. Front Immunol. 2024 Sep 23;15:1461756. doi: 10.3389/fimmu.2024.1461756. PMID: 39376556; PMCID: PMC11456432.
8. Masuko K. Cigarette Smoking: A Modifiable Environmental Factor in the Pathogenesis of Rheumatoid Arthritis. JMA J. 2025 Oct 15;8(4):1077-1086. doi: 10.31662/jmaj.2025-0029. Epub 2025 Oct 3. PMID: 41220506; PMCID: PMC12598268.
9. Baka Z, Buzás E, Nagy G. Rheumatoid arthritis and smoking: putting the pieces together. Arthritis Res Ther. 2009;11(4):238. doi: 10.1186/ar2751. Epub 2009 Aug 3. PMID: 19678909; PMCID: PMC2745780.
10. Harrison SR, Jutley G, Li D, Sahbudin I, Filer A, Hewison M, Raza K. Vitamin D and early rheumatoid arthritis. BMC Rheumatol. 2020 Jul 27;4:38. doi: 10.1186/s41927-020-00134-7. PMID: 32728658; PMCID: PMC7384217.
11. Yang L, Zhao H, Liu K, Wang Y, Liu Q, Sun T, Chen S, Ren L. Smoking behavior and circulating vitamin D levels in adults: A meta-analysis. Food Sci Nutr. 2021 Aug 5;9(10):5820-5832. doi: 10.1002/fsn3.2488. PMID: 34646549; PMCID: PMC8497833.
12. Lee H, Kim KN, Lim YH, Hong YC. Interaction of Vitamin D and Smoking on Inflammatory Markers in the Urban Elderly. J Prev Med Public Health. 2015 Sep;48(5):249-56. doi: 10.3961/jpmph.15.042. Epub 2015 Sep 17. PMID: 26429291; PMCID: PMC4592026.
13. Kostoglou-Athanassiou I, Athanassiou P, Lyraki A, Raftakis I, Antoniadis C. Vitamin D and rheumatoid arthritis. Ther Adv Endocrinol Metab. 2012 Dec;3(6):181-7. doi: 10.1177/2042018812471070. PMID: 23323190; PMCID: PMC3539179.
14. Chang K, Yang SM, Kim SH, Han KH, Park SJ, Shin JI. Smoking and rheumatoid arthritis. Int J Mol Sci. 2014 Dec 3;15(12):22279-95. doi: 10.3390/ijms151222279. PMID: 25479074; PMCID: PMC4284707.
15. Noorwali AA. Comorbidities in smoking and nonsmoking male Saudi patients with rheumatoid arthritis. Int J Biol Biotech. 2023;20 (23): 195-99.
16. Noorwali AA. Serum vitamin-D inversely associates with the duration of disease in male patients with rheumatoid arthritis. Int J Biol Biotech. 2023;20 (2): 201-06.
17. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. Mayo Clin Proc. 2010 Aug;85(8):752-7; quiz 757-8. doi: 10.4065/mcp.2010.0138. PMID: 20675513; PMCID: PMC2912737.
18. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jul;96(7):1911-30. doi: 10.1210/jc.2011-0385. Epub 2011 Jun 6. Erratum in: J Clin Endocrinol Metab. 2011 Dec;96(12):3908. Erratum in: J Clin Endocrinol Metab. 2024 Sep 16;109(10):e1991. doi: 10.1210/clinem/dgae373. PMID: 21646368.
19. Kaur J, Khare S, Givler A. Vitamin D Deficiency. 2025 Feb 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan–. PMID: 30335299.
20. Bordelon P, Ghetu MV, Langan RC. Recognition and management of vitamin D deficiency. Am Fam Physician. 2009 Oct 15;80(8):841-6. Erratum in: Am Fam Physician. 2009 Dec 15;80(12):1357. PMID: 19835345.
21. Boucher BJ. The problems of vitamin d insufficiency in older people. Aging Dis. 2012 Aug;3(4):313-29. Epub 2012 Jun 6. PMID: 23185713; PMCID: PMC3501367.
22. Lange NE, Sparrow D, Vokonas P, Litonjua AA. Vitamin D deficiency, smoking, and lung function in the Normative Aging Study. Am J Respir Crit Care Med. 2012 Oct 1;186(7):616-21. doi: 10.1164/rccm.201110-1868OC. Epub 2012 Jul 19. PMID: 22822023; PMCID: PMC3480523.
23. Koçak MB, Kavuncuoğlu D. The relationship between smoking cessation and vitamin D. Ir J Med Sci. 2026 Apr;195(2):1165-1172. doi: 10.1007/s11845-026-04290-6. Epub 2026 Feb 28. PMID: 41762403; PMCID: PMC13190799.
24. Jiang CQ, Chan YH, Xu L, Jin YL, Zhu T, Zhang WS, Cheng KK, Lam TH. Smoking and serum vitamin D in older Chinese people: cross-sectional analysis based on the Guangzhou Biobank Cohort Study. BMJ Open. 2016 Jun 23;6(6):e010946. doi: 10.1136/bmjopen-2015-010946. PMID: 27338881; PMCID: PMC4932269.
25. Nwosu BU, Kum-Nji P. Tobacco smoke exposure is an independent predictor of vitamin D deficiency in US children. PLoS One. 2018 Oct 8;13(10):e0205342. doi: 10.1371/journal.pone.0205342. PMID: 30296288; PMCID: PMC6175516.
26. Yang L, Sato M, Saito-Abe M, Miyaji Y, Sato C, Nishizato M, Kumasaka N, Mezawa H, Yamamoto-Hanada K, Ohya Y. Smoking Exposure Is Associated with Serum Vitamin D Deficiency in Children: Evidence from the Japan Environment and Children's Study. Nutrients. 2022 Jul 29;14(15):3121. doi: 10.3390/nu14153121. PMID: 35956297; PMCID: PMC9370804.
27. Yuan L, Ni J. The association between tobacco smoke exposure and vitamin D levels among US general population, 2001-2014: temporal variation and inequalities in population susceptibility. Environ Sci Pollut Res Int. 2022 May;29(22):32773-32787. doi: 10.1007/s11356-021-17905-5. Epub 2022 Jan 12. PMID: 35020139; PMCID: PMC8752386.
28. Okrit F, Chantranuwatana P, Werawatganon D, Chayanupatkul M, Sanguanrungsirikul S. Changes of vitamin D receptors (VDR) and MAPK activation in cytoplasmic and nuclear fractions following exposure to cigarette smoke with or without filter in rats. Heliyon. 2021 Jan 30;7(1):e05927. doi: 10.1016/j.heliyon.2021.e05927. PMID: 33553726; PMCID: PMC7851787.
29. Voltan G, Cannito M, Ferrarese M, Ceccato F, Camozzi V. Vitamin D: An Overview of Gene Regulation, Ranging from Metabolism to Genomic Effects. Genes (Basel). 2023 Aug 25;14(9):1691. doi: 10.3390/genes14091691. PMID: 37761831; PMCID: PMC10531002.
30. Al-Bashaireh AM, Haddad LG, Weaver M, Chengguo X, Kelly DL, Yoon S. The Effect of Tobacco Smoking on Bone Mass: An Overview of Pathophysiologic Mechanisms. J Osteoporos. 2018 Dec 2;2018:1206235. doi: 10.1155/2018/1206235. PMID: 30631414; PMCID: PMC6304634.
31. Mulligan JK, Nagel W, O'Connell BP, Wentzel J, Atkinson

C, Schlosser RJ. Cigarette smoke exposure is associated with vitamin D3 deficiencies in patients with chronic rhinosinusitis. J Allergy Clin Immunol. 2014 Aug;134(2):342-9. doi: 10.1016/j.jaci.2014.01.039. Epub 2014 Mar 31. PMID: 24698317.
32. Azzeh FS, Kensara OA. Vitamin D Is a Good Marker for Disease Activity of Rheumatoid Arthritis Disease. Dis Markers. 2015;2015:260725. doi: 10.1155/2015/260725. Epub 2015 May 10. PMID: 26063950; PMCID: PMC4441987.
33. Lee YH, Bae SC. Vitamin D level in rheumatoid arthritis and its correlation with the disease activity: a meta-analysis. Clin Exp Rheumatol. 2016 Sep-Oct;34(5):827-833. Epub 2016 Apr 6. PMID: 27049238.
34. Guan Y, Hao Y, Guan Y, Bu H, Wang H. The Effect of Vitamin D Supplementation on Rheumatoid Arthritis Patients: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2020 Oct 30;7:596007. doi: 10.3389/fmed.2020.596007. PMID: 33195358; PMCID: PMC7661491.
35. Khatirnamani Z, Hajian-Tilaki K, Heidari B, Sohrabi A. The Effect of Vitamin D Supplementation on Clinical and Laboratory Biomarkers in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. Mediterr J Rheumatol. 2025 Sep 30;36(3):428-439. doi: 10.31138/mjr.090725.lar. PMID: 41122185; PMCID: PMC12536741.
36. Vidal M, Lane NE. Vitamin D and Its Role in Rheumatic Diseases. Metabolites. 2025 Apr 9;15(4):259. doi: 10.3390/metabo15040259. PMID: 40278388; PMCID: PMC12029499.
37. Kwon OC, Oh JS, Park MC, Kim YG. Effect of Vitamin D Supplementation on Bone Mineral Density in Rheumatoid Arthritis Patients With Osteoporosis. Front Med (Lausanne). 2020 Aug 21;7:443. doi: 10.3389/fmed.2020.00443. PMID: 32974365; PMCID: PMC7473387.
38. Bellan M, Sainaghi PP, Pirisi M. Role of Vitamin D in Rheumatoid Arthritis. Adv Exp Med Biol. 2017;996:155-168. doi: 10.1007/978-3-319-56017-5_13. PMID: 29124698.
39. Meena N, Singh Chawla SP, Garg R, Batta A, Kaur S. Assessment of Vitamin D in Rheumatoid Arthritis and Its Correlation with Disease Activity. J Nat Sci Biol Med. 2018 Jan-Jun;9(1):54-58. doi: 10.4103/jnsbm.JNSBM_128_17. PMID: 29456394; PMCID: PMC5812075.
40. Mukherjee D, Lahiry S, Thakur S, Chakraborty DS. Effect of 1,25 dihydroxy vitamin D3 supplementation on pain relief in early rheumatoid arthritis. J Family Med Prim Care. 2019 Feb;8(2):517-522. doi: 10.4103/jfmpc.jfmpc_446_18. PMID: 30984665; PMCID: PMC6436291.
41. Alharbi S, Alharbi R, Alhabib E, Ghunaim R, Alreefi MM. Vitamin D Deficiency in Saudi Patients With Rheumatoid Arthritis. Cureus. 2023 Feb 9;15(2):e34815. doi: 10.7759/cureus.34815. PMID: 36793500; PMCID: PMC9924707.
42. Attar SM. Vitamin D deficiency in rheumatoid arthritis. Prevalence and association with disease activity in Western Saudi Arabia. Saudi Med J. 2012 May;33(5):520-5. PMID: 22588813.
43. Rossini M, Maddali Bongi S, La Montagna G, Minisola G, Malavolta N, Bernini L, Cacace E, Sinigaglia L, Di Munno O, Adami S. Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants and associations with disease activity and disability. Arthritis Res Ther. 2010;12(6):R216. doi: 10.1186/ar3195. Epub 2010 Nov 29. PMID: 21114806; PMCID: PMC3046526.
44. Lin J, Liu J, Davies ML, Chen W. Serum Vitamin D Level and Rheumatoid Arthritis Disease Activity: Review and Meta-Analysis. PLoS One. 2016 Jan 11;11(1):e0146351. doi: 10.1371/journal.pone.0146351. PMID: 26751969; PMCID: PMC4709104.
45. Aslam MM, John P, Bhatti A, Jahangir S, Kamboh MI. Vitamin D as a Principal Factor in Mediating Rheumatoid Arthritis-Derived Immune Response. Biomed Res Int. 2019 May 7;2019:3494937. doi: 10.1155/2019/3494937. PMID: 31205940; PMCID: PMC6530219.
46. Charoenngam N. Vitamin D and Rheumatic Diseases: A Review of Clinical Evidence. Int J Mol Sci. 2021 Oct 1;22(19):10659. doi: 10.3390/ijms221910659. PMID: 34639000; PMCID: PMC8508879.
47. Clasen JL, Cole R, Aune D, Sellon E, Heath AK. Vitamin D status and risk of rheumatoid arthritis: systematic review and meta-analysis. BMC Rheumatol. 2023 Mar 15;7(1):3. doi: 10.1186/s41927-023-00325-y. PMID: 36918989; PMCID: PMC10015722.
48. Rexhepi M, Krasniqi B, Hoti K, Daci A, Rexhepi-Kelmendi B, Krasniqi S. Impact of vitamin D supplementation on disease activity and pain management in rheumatoid arthritis: a randomized double-blinded controlled study. BMC Rheumatol. 2025 Jul 11;9(1):87. doi: 10.1186/s41927-025-00543-6. PMID: 40646666; PMCID: PMC12247244.
49. Elfituri S. The effects of vitamin D supplementation on disease activity and fatigue in Libyan rheumatoid arthritis patients. Reumatologia. 2024;62(2):109-114. doi: 10.5114/reum/187391. Epub 2024 May 10. PMID: 38799782; PMCID: PMC11114129.
50. Ranjbar M, Rahimlou M, Fallah M, Djafarian K, Mohammadi H. Effects of vitamin D supplementation in patients with rheumatoid arthritis: A systematic review and meta-analysis. Heliyon. 2025 Feb 4;11(3):e42463. doi: 10.1016/j.heliyon.2025.e42463. PMID: 39995929; PMCID: PMC11849653.
51. Sukharani N, Dev K, Rahul F, Bai P, Ali A, Avinash F, Kammawal Y, Kumar N, Rizwan A. Association Between Rheumatoid Arthritis and Serum Vitamin D Levels. Cureus. 2021 Sep 24;13(9):e18255. doi: 10.7759/cureus.18255. PMID: 34712532; PMCID: PMC8542394.
52. Hussain MS, Islam T, Islam MS, Danishuddin, Haque MA. Clinical insights into the role of smoking, diabetes, and rheumatoid arthritis in osteoporotic fractures. Arch Osteoporos. 2025 Jul 11;20(1):87. doi: 10.1007/s11657-025-01575-8. PMID: 40643730.
53. Hajjaj-Hassouni N, Mawani N, Allali F, Rkain H, Hassouni K, Hmamouchi I, Dougados M. Evaluation of Vitamin D Status in Rheumatoid Arthritis and Its Association with Disease Activity across 15 Countries: "The COMORA Study". Int J Rheumatol. 2017;2017:5491676. doi: 10.1155/2017/5491676. Epub 2017 Jun 1. PMID: 28656048; PMCID: PMC5471553.
54. Batista AAP, Lazzarin T, Pereira FWL, Baccaro A, Rocha OM, Narimatsu KL, Souza JT, Modesto PN, Zanati Bazan SG, Tanni SE, Okoshi MP, Polegato BF, Paiva SAR, Zornoff L, Minicucci MF, Azevedo PS. Serum Vitamin D Levels, Disease Activity Score-28 for Rheumatoid Arthritis with C-Reactive Protein (DAS28-CRP), and Cardiac Remodeling Determined by Ventricular Dimensions and Left Atrium Diameter in Patients with Rheumatoid Arthritis: A Prospective Observational Study. Med Sci Monit. 2023 Jan 7;29:e938989. doi: 10.12659/MSM.938989. PMID: 36609557; PMCID: PMC9832721.