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# Vitamin D3: Role in Chronic Inflammatory Disorders

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## ABSTRACT

**Background:** Vitamin D3 (Calcitriol) plays a pivotal role in regulating immune function and mitigating chronic inflammation. Its immunomodulatory effects contribute to improved outcomes in autoimmune and inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, polycystic ovarian syndrome, and inflammatory bowel disease.

**Methods:** This review synthesizes current evidence from 46 articles published between 2006 and 2025, from experimental, clinical, and randomized controlled trials examining the immunological effects, optimal dosing, and safety of Vitamin D3 supplementation in chronic inflammatory conditions.

**Results:** Vitamin D3 modulates both innate and adaptive immunity by enhancing antimicrobial peptide production and promoting mucosal integrity. It induces regulatory T cells while suppressing pro-inflammatory Th1 and Th17 subsets, decreasing levels of IL-6, TNF-α, IL-17, and IFN-γ and increasing IL-10 and TGF-β. Clinical studies demonstrate inverse associations between serum 25(OH)D levels and inflammatory markers such as high-sensitivity C-Reactive Protein (hsCRP) and Neutrophil-To-Lymphocyte Ratio (NLR). Supplementation of 1000–4000 IU/day maintains optimal serum concentrations (30–60 ng/mL; 75–150 nmol/L), with the best anti-inflammatory effects observed near 36–40 ng/mL. Correcting deficiency (<25–30 nmol/L) yields the most significant clinical benefits, while benefits plateau beyond 75 nmol/L. Toxicity and hypercalcemia are rare below 100 ng/mL (250 nmol/L), and routine supplementation remains safe under medical supervision.

**Conclusion:** Maintaining serum 25(OH)D levels between 30–60 ng/mL through daily Vitamin D3 supplementation (1000–4000 IU) effectively reduces systemic inflammation and enhances immune regulation. This strategy represents a safe and beneficial adjunct in managing chronic inflammatory and autoimmune diseases.

**Keywords:** Vitamin D3; Calcitriol; Inflammation; Chronic disease; Mechanism of action; Biomarkers; Supplementation; RCTs

## INTRODUCTION

Vitamin $D_3$ (Vit D), classically recognized for its pivotal role in calcium and phosphate metabolism and bone health, has emerged as a pleiotropic hormone influencing immune function, inflammation, and chronic disease pathophysiology. The active metabolite,1,25-dihydroxyvitamin $D_3$ (calcitriol), binds to nuclear vitamin D Receptors (VDRs) distributed across various tissues, including immune, cardiovascular, and endocrine systems. Through genomic and non-genomic pathways, it orchestrates a diverse array of biological functions extending far beyond skeletal maintenance.

Recent literature underscores vitamin D's potential as a modulator of systemic inflammation and a preventive or adjunctive therapy for chronic inflammatory diseases. This review synthesizes empirical findings from over forty primary studies and clinical guidelines published between 2006 and 2025 to examine the anti-inflammatory, immunomodulatory, and therapeutic implications of vitamin D supplementation.

## LITERATURE REVIEW

### Physiological and molecular mechanisms of vitamin D in immunoregulation

Vitamin D mediates immune responses predominantly through its receptor (VDR), expressed in antigen-presenting cells (macrophages and dendritic cells), as well as T and B lymphocytes.

The engagement of calcitriol with VDR results in transcriptional regulation of more than 200 genes associated with immune, metabolic, and inflammatory processes [1].

Shrivastava and Leal demonstrated that vitamin D regulates redox balance and attenuates pro-inflammatory cytokines, including IL-6, TNF-α, and IL-17, while enhancing the expression of anti-inflammatory IL-10 and TGF-β. Importantly, highlighted its function in stabilizing the NF-κB signaling cascade—a hallmark of inflammatory activation-by promoting the synthesis of IκBα, which inhibits NF-κB nuclear translocation [2,3].

Vitamin D also enhances innate immunity by upregulating antimicrobial peptides, notably cathelicidin and defensins, which provide first-line defense against microbial invasion [4]. Collectively, the immunological pathways explain the observed protective effects against autoimmune diseases, respiratory infections, and systemic inflammatory conditions.

### Global burden of vitamin D deficiency

Despite its physiological importance, vitamin D deficiency remains a global health issue. Amrein et al, reported that approximately 40% of the global population has serum 25-hydroxyvitamin D [25(OH)D] deficiency levels of below 20 ng/mL, with even higher prevalence in individuals with darker skin, limited sun exposure, and high-latitude residence [5].

The deficiency's broad clinical consequences encompass not only osteoporosis and rickets but also increased susceptibility to metabolic syndrome, type 2 diabetes mellitus, cardiovascular diseases, and autoimmune disorders [6]. Banerjee and Banerjee described how chronic inflammation, partly driven by hormonal and metabolic dysregulation, is exacerbated by inadequate vitamin D status-highlighting its role as both a preventive and therapeutic nutrient in polycystic ovarian syndromes [7].

### Vitamin D and inflammatory biomarkers

Epidemiological and clinical studies consistently demonstrate inverse associations between circulating 25(OH)D concentrations and proinflammatory markers. Kruit and Zanen, et al. found that higher vitamin D status correlates with lower C-Reactive Protein (CRP) levels in both inflammatory and non-inflammatory disease cohorts [8]. De Vita et al, confirmed that older adults with sufficient vitamin D presented with reduced TNF-α and IL-6 [9].

Recent pediatric evidence by Carboo et al, reinforced these findings: children maintaining adequate 25(OH)D exhibited diminished systemic and intestinal inflammation compared to undernourished peers [10]. Pasupulati et al, demonstrated that oral vitamin D supplementation in type 2 diabetes significantly lowered hsCRP, IL-6, and fibrinogen, reflecting an attenuation of oxidative and inflammatory stress [11].

Mechanistically, these effects are attributed to the suppression of the NF-κB and JAK/STAT signaling pathways, coupled with modulation of macrophage activation and oxidative enzyme activity [12] (Figure 1).

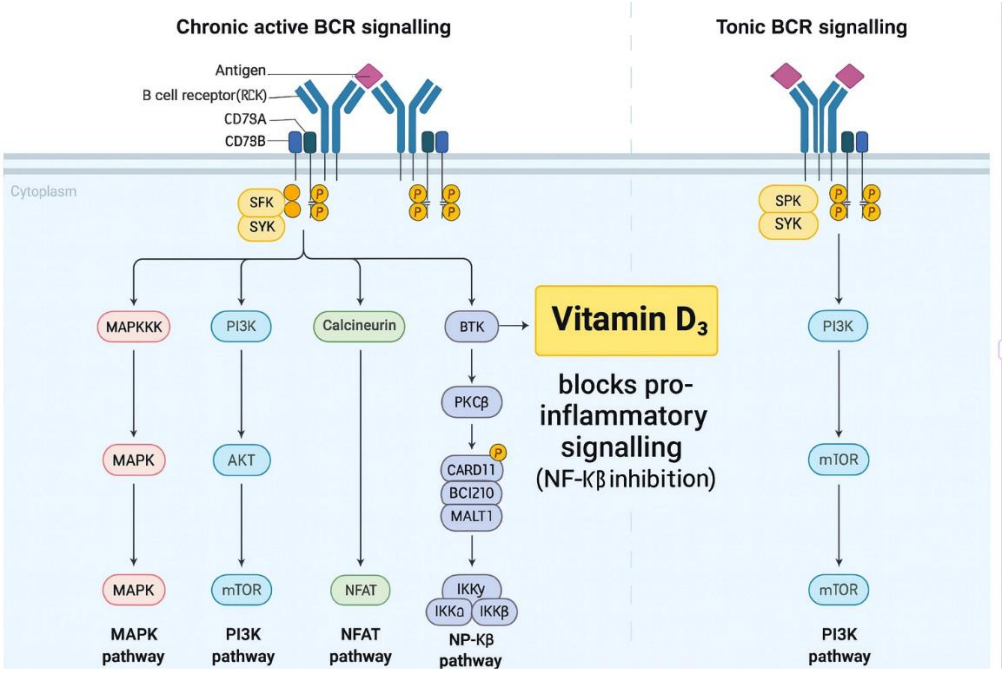


**Figure 1:** Mechanism of action of vitamin D3 in immunomodulatory pathways [12].

## Anti-inflammatory and immunomodulatory evidence (2020–2025)

**Recent clinical and preclinical studies further confirm the anti-inflammatory function of vitamin D:**

Alsufiani et al, showed that a single oral bolus of vitamin $D_3$ caused significant reductions in CRP and IL-6 in healthy Saudi males, implying that even acute supplementation elicits rapid immune modulation [13]. Mousa and Zughaier et al, established that vitamin D deficiency disrupts HDL-associated anti-inflammatory proteins such as ApoA-1 and ApoM, culminating in lower anti-inflammatory potential [14]. Adequate vitamin D preserves lipid-mediated immune balance, linking deficiency with both vascular and inflammatory risk. Mokgalaboni et al, described consistent inhibition of NF-κB, TNF-α, and MCP-1 in rodent models, though clinical translation remains partial [15]. Srivastava et al, in a meta-analysis—showed that vitamin $D_3$ supplementation in autoimmune disorders such as rheumatoid arthritis (RA) and multiple sclerosis (MS) led to significant decreases in IL-6, TNF-α, and IFN-γ, with parallel increases in IL-10 [2].

Overall, the evidence reinforces vitamin D's systemic immunoregulatory effects across diverse biological systems.

## Vitamin D in Endocrine, Metabolic, and Immune-Related Disorders

### Metabolic and Endocrine Health

Vitamin D contributes to metabolic homeostasis by modulating pancreatic β-cell function and insulin sensitivity. Arabi et al. (2024) identified a crucial interaction between vitamin D deficiency, low-grade inflammation, and prediabetes, suggesting that supplementation may delay progression to diabetes [16]. Further found reductions in fibrinogenic and inflammatory markers in diabetic patients receiving vitamin D supplementation [10].

### Autoimmune and inflammatory diseases

RCTs across autoimmune diseases consistently report anti-inflammatory effects. Srivastava et al, documented significant decreases in IL-6, TNF-α, and IFN-γ, coupled with improved clinical outcomes, especially in multiple sclerosis and rheumatoid arthritis [2]. Similarly, Crotti et al, and Krajewska et al, observed mitigation of obesity-related inflammation and spondyloarthritis symptoms after vitamin D therapy [17,18].

### Infectious and COVID-19 settings

The COVID-19 pandemic intensified research interest in vitamin D's immune benefits. Halim et al, established inverse correlations between baseline

25(OH)D levels and pro-inflammatory cytokines (IL-6, TNF-α), linking higher vitamin D levels with reduced severity and mortality [19]. Harvard and NIH fact sheets (2025) confirm ongoing investigations linking deficiency to poor respiratory outcomes [20].

Vitamin D's promotion of innate antimicrobial pathways, suppression of cytokine storms, and enhancement of epithelial integrity collectively explain these observed protective trends.

## DISCUSSION

### Recent clinical trials and meta-analyses

A landmark umbrella meta-analysis by demonstrated that vitamin D supplementation consistently improved inflammatory biomarkers and oxidative stress markers across diverse diseases [21].

The VITAL trial (Scientific American, 2025) reported that long-term daily supplementation led to a 19–22% reduction in autoimmune disease incidence, though the effect on CRP waned after four years, suggesting a threshold benefit rather than progressive improvement [22].

Another meta-analysis synthesized by Srivastava et al, found that individuals with adequate vitamin D levels were 30–40% less likely to suffer severe infectious diseases, reaffirming vitamin D's role in maintaining immune resilience [2].

### Dosing principles and supplementation algorithms

### Evidence-based dosing frameworks

Bleizgys presented a holistic, individualized dosing algorithm considering serum 25(OH)D baseline, body weight, absorption rate, and clinical goal. Typical sufficiency targets range from 30–50 ng/mL [23-25].

McCullough et al, validated the safety of high long-term doses (up to 50,000 IU/day) under clinical supervision. For general wellness, cohort-based studies indicate that 2000–4000 IU/day sustains serum concentrations of 40–70 ng/mL-levels associated with maximal anti-inflammatory and systemic protection [25,26].

### Updated guidelines

Recent guidelines from the Endocrine Society (2024) and NIH (2025) codify age- and risk-adjusted recommendations (Table 1).

**Table 1:** Age-appropriate dietary recommendations in various chronic diseases.

| Age Group | Recommended Intake | Target Serum 25(OH)D | Reference |
|---|---|---|---|
| 0–12 months | 400 IU/day | >20 ng/mL | NIH, 2025 |
| 1–70 years | 600 IU/day | >30 ng/mL | NIH, 2025 |
| >70 years | 800–2000 IU/day | 30–50 ng/mL | NIH/Endocrine, 2025 |
| At-risk populations | 2000–4000 IU/day | 40–70 ng/mL | Giustina et al., 2024 |

The bpac (2025) update endorsed prophylactic supplementation for all exclusively or partly breastfed infants, emphasizing decreasing sunlight exposure due to UV-avoidance practices.

### Adverse effects and safety considerations

While vitamin D is generally safe, excessive supplementation (>10,000 IU/day) can provoke hypercalcemia, vascular calcification, and renal injury (Harvard, 2025). The NIH (2025) identifies serum levels >125 nmol/L (≈50 ng/mL) as potentially harmful. Nonetheless, McCullough and Grant reported no toxicity at supervised daily intakes of ≤6000 IU/day [25,26].

The consensus conclusion: vitamin D exhibits a "U-shaped" response, where deficiency exacerbates inflammation and excessive intake induces toxicity through dysregulated calcium–phosphate metabolism.

### Vitamin D and bone-immune axis integration

The classical skeletal benefits remain integral. Demonstrated fracture risk reduction at serum concentrations above 30 ng/mL. Macdonald et al, confirmed a plateau effect around 40 ng/mL, suggesting that beyond this, bone benefits do not increase further [27,28].

Newer evidence suggests that these same thresholds align with optimal anti-inflammatory profiles, confirming interconnected bone and immune health pathways regulated via VDR-mediated gene expression [25].

## Vitamin D's role in lipid and cardiovascular health

Emerging mechanistic insights connect vitamin D with lipid-mediated anti-inflammatory pathways. Mousa and Zughaier found that deficiency impairs HDL functionality through apoenzyme depletion (ApoA-1, ApoM, ApoD), thereby diminishing HDL's anti-inflammatory and antioxidant properties [29]. This crosstalk between lipid metabolism and inflammatory signaling provides new mechanistic bases for vitamin D's cardioprotective actions.

## Vitamin D as a pharmacological candidate

An evolving area of therapeutics conceptualizes "vitamin D as a drug", extending its use beyond supplementation [30]. Novel vitamin D analogs are being developed to maximize immune and anti-inflammatory efficacy while minimizing hypercalcemia. Early trials in autoimmune and neoplastic conditions exhibit promising outcomes, advocating renewed pharmaceutical exploration.

## Interrelationship between vitamin D and nutritional health

Vitamin D bioavailability and metabolic efficiency depend on interplay with dietary fat, gut health, and cofactors such as magnesium. Underline that comprehensive nutritional strategies—combining vitamin D with calcium and omega-3 fatty acids—are essential for sustained anti-inflammatory and metabolic benefits [31].

## Threshold concepts and epidemiologic evidence

Scragg and Bischoff-Ferrari et al, proposed that benefits plateau beyond a serum threshold of roughly 40 ng/mL. Below 20 ng/mL, the risk of chronic diseases rises sharply [32,33]. Newer evaluations advocate broader targets (40–70 ng/mL) for optimal extra-skeletal outcomes [25]. Nonetheless, the consensus remains that more is not always better; individualized titration is critical.

## Sociodemographic and regional considerations

Global heterogeneity influences deficiency patterns and supplementation policy. Articulated region-specific Polish recommendations, emphasizing latitude, phototype, and dietary variation [18]. Reinforced this tailored approach, calling for revised models that integrate ethnicity, BMI, and environmental exposure as covariates in dosing calculations [24].

## Future directions and research gaps

Despite overwhelming observational and mechanistic evidence, randomized controlled trials still produce inconsistent outcomes. These discrepancies likely stem from variations in baseline vitamin D status, short intervention durations, and lack of stratified dosing. Future studies should employ precision-medicine frameworks incorporating genomic polymorphisms (VDR, CYP genes), dynamic dosing, and systems biology analytics to refine supplementation protocols.

## Dietary recommendations

A meal plan focused on fatty fish, eggs, fortified foods, and mushrooms, spread over 8 weeks, is most effective for raising vitamin D3 levels. Fatty fish and eggs should appear multiple times per week, along with fortified dairy/alternatives and UV-exposed mushrooms for best results.

Key daily food sources

- Fatty fish (salmon, sardines, mackerel, tuna) at least 2–3 times per week.
- Egg yolks as part of breakfast or lunch, about 4–5 times per week.
- Fortified milk, plant milks, or yogurt every day.
- UV-exposed mushrooms several times a week, in salads, stir-fries, or omelets.

Oily fish curries or grilled fish as a protein source in main meals.

Fortified breakfast cereals, tofu, and orange juice supporting the plan.

## Sample week (repeat for 8 Weeks)

Use cod liver oil in salad dressings occasionally for added boost. Maintain variety by rotating fish, eggs, and mushrooms in different dishes.

Avoid excess fried food and sugar; emphasize whole, nutritious ingredients. Drink fortified milk or its alternatives at breakfast and/or evening.

Repeating this plan over 8 weeks, with focus on these foods, is highly effective for raising vitamin D3 levels along with moderate sun exposure, whenever possible.

## CONCLUSION

From fundamental molecular mechanisms to population-level meta-analyses, the collective body of evidence affirms that vitamin D plays a crucial anti-inflammatory and immunomodulatory role. Adequate 25(OH)D levels (30–50 ng/mL) are consistently associated with:

- Suppression of IL-6, TNF-α, and CRP
- Enhanced IL-10 and TGF-β expression
- Improved endothelial, metabolic, and lipid profiles
- Lower incidence of autoimmune and infectious diseases

Yet, the clinical magnitude of benefit depends on initial deficiency, dose, and population demographics. Excessive supplementation undermines safety, while personalized regimens-anchored in serum monitoring and evidence-based guidelines-optimize benefits.

In summary, vitamin D transcends its historical role as a "bone vitamin," emerging as a central endocrine regulator of inflammation, metabolism, and immune homeostasis. Integrating its assessment and rational supplementation into global public health strategies offers a pragmatic, low-cost intervention against chronic inflammatory disease.

## DECLARATIONS

### Conflict of interest

The author declares that there are no competing interests.


### Funding

The author declares that no external funding was received for this study.


### Author Contributions (CRediT Taxonomy):

**Arnav Roy:** Conceptualization, Literature Review, Investigation, Data Curation, Writing – Original Draft.

**Romi Banerjee:** Methodology, Formal Analysis, Visualization, Writing – Review & Editing.

**Abhijit G. Banerjee:** Supervision, Project Administration, Validation, Writing – Review & Editing, Funding Acquisition.

### Ethical approval

Not applicable. This study did not involve human participants or animals, and no ethical approval was required.

### Consent for publication

Not applicable. The manuscript does not contain any individual person's data in any form (including images, videos, or personal details).

### Availability of data and materials

All data generated or analysed during this study are included in this published article. Additional information can be provided by the corresponding author upon reasonable request.


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