

High-Dose Vitamin D in Autoimmune Rheumatologic Disease: A Five-Condition Review

Bottom line up front: Across psoriatic arthritis (PsA), rheumatoid arthritis (RA), spondyloarthritis (SpA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc), serum 25(OH)D is consistently 7–12 ng/mL lower than in matched controls and is *inversely correlated* with every major activity score (DAS28, BASDAI, SLEDAI, PASI/DAPSA, modified Rodnan skin score). The strongest interventional signal comes from SLE — where bolus doses of 100,000 IU/week followed by 100,000 IU/month restore Treg/Th17 balance, lower anti-dsDNA, and reduce SLEDAI — and from the VITAL prevention trial, in which 2,000 IU/day for 5.3 years reduced *incident* autoimmune disease by 22%. RA meta-analyses show clear improvement in pain (VAS) and CRP with supplementation, but DAS28 effects only emerge with longer duration and higher doses. Evidence for AS and SSc is dominated by observational data with notably few high-dose RCTs. The Coimbra Protocol (~30,000–60,000 IU/day with strict calcium restriction) reports favorable safety in 319 patients over 3.5 years but lacks controlled efficacy data for the rheumatologic conditions specifically. [\(Substack\)](#)

Introduction — Shared Autoimmune Mechanism

The five conditions reviewed are mechanistically united by an imbalance between pro-inflammatory effector T cells (Th1/Th17) and regulatory T cells (Treg), with disease-specific contributions from B cells (especially SLE) and fibroblasts (especially SSc). 1,25-dihydroxyvitamin D₃ (calcitriol) acts as a ligand for the vitamin D receptor (VDR), which is expressed on virtually every cell of the adaptive and innate immune system — including activated CD4⁺ Th cells, CD8⁺ cytotoxic T cells, B cells, dendritic cells, macrophages, and synovial fibroblasts.

Key immunologic actions of calcitriol relevant to all five diseases:

- **Th17 suppression / Treg expansion.** Calcitriol inhibits IL-17 production by Th17 cells (via blockade of NFAT, recruitment of HDAC, and Runx1 sequestration), and induces FoxP3⁺ Tregs producing IL-10 and TGF-β. In the EAE multiple-sclerosis model, calcitriol's effects depend entirely on IL-10 signaling. [\(NCBI + 2\)](#)
- **Dendritic cell tolerogenesis.** Calcitriol-conditioned dendritic cells down-regulate MHC II, decrease IL-12, and increase IL-10, biasing T-cell priming away from Th1/Th17 and toward Treg. [\(PubMed Central\)](#) [\(PubMed Central\)](#)
- **B-cell restraint.** VDR activation inhibits plasma-cell differentiation and autoantibody secretion — directly relevant to lupus, where memory B cells and anti-dsDNA fall with supplementation. [\(PubMed Central\)](#)
- **Anti-fibrotic action.** Calcitriol and the VDR agonist paricalcitol form complexes with phosphorylated SMAD3, blocking TGF-β-driven collagen transcription. VDR expression is

paradoxically *reduced* in SSc fibroblasts in a TGF- β -dependent feed-forward loop (Zerr et al., *Ann Rheum Dis* 2014). [PubMed](#) [PubMed](#)

- **Local 1 α -hydroxylation.** Macrophages, synoviocytes, and dendritic cells express CYP27B1 and convert 25(OH)D to calcitriol intracrinally. Substrate (circulating 25(OH)D) availability — not just renal calcitriol — is rate-limiting.

Why higher-than-standard dosing may be required in active autoimmunity. Several biologic factors converge to raise the effective vitamin D requirement of patients with the five diseases reviewed:

1. **Inflammation-driven catabolism.** TNF- α and IL-1 β up-regulate CYP24A1 (24-hydroxylase), the enzyme that degrades both 25(OH)D and calcitriol to inactive metabolites. Active RA, SLE, and SSc therefore "burn through" vitamin D faster.
2. **Glucocorticoid effects.** Chronic prednisone use roughly *doubles* the risk of 25(OH)D < 25 nmol/L (Skversky et al., NHANES 2001–2006); steroids induce CYP24A1 and impair intestinal calcium/vitamin D handling. [ScienceDirect](#)
3. **VDR polymorphisms.** FokI, BsmI, TaqI, and ApaI variants alter VDR function and have been linked to susceptibility for RA, SLE, AS, and SSc.
4. **Vitamin D-binding protein (DBP/GC) polymorphisms.** Modify bioavailable fraction of 25(OH)D delivered to immune cells.
5. **"Acquired vitamin D resistance"** hypothesis (Lemke et al., *Front Immunol* 2021) — the theoretical basis of the Coimbra Protocol — proposing that effective intracellular VDR signaling in autoimmune patients requires substantially higher 25(OH)D substrate than in healthy individuals. [ResearchGate](#)
6. **Sun avoidance** is enforced in SLE (photosensitivity) and is common in SSc (Raynaud's, skin involvement) and the chronic-disease populations generally, lowering endogenous synthesis.

These mechanistic considerations make a priori plausible that standard "bone-health" doses (600–800 IU/day) and the 30 ng/mL threshold are *insufficient* in active rheumatic disease, and they motivate the interventional trials and protocols summarized below.

1. Rheumatoid Arthritis (RA)

Epidemiology of vitamin D status in RA

Vitamin D deficiency is consistently more prevalent in RA patients than in matched controls. A 2024 EULAR-cited meta-analysis of 15 case-control studies (1,143 RA patients, 963 controls) and earlier work confirm a substantial deficit. Cross-sectional studies repeatedly show inverse correlations between serum 25(OH)D and DAS28, HAQ, and Sharp van der Heijde joint destruction score, although associations with TNF- α , CRP, and ESR are inconsistent across smaller studies. Patients on biologics tend to have lower 25(OH)D than those on conventional

DMARDs, partly reflecting more severe baseline disease and partly reflecting steroid co-exposure. [nih + 2](#)

High-dose interventional data in RA

Andjelkovic et al. (Clin Exp Rheumatol 1999) — A pioneering open-label trial of high-dose $1\alpha(\text{OH})\text{D}_3$ (alfacalcidol, 2 $\mu\text{g}/\text{day}$ for 3 months) in 19 patients with active, treatment-refractory RA reported clinical improvement in 89% with "complete remission" in 45% — providing the historical basis for the high-dose hypothesis. Limited by small size and open-label design, but mechanistically informative because alfacalcidol bypasses 25-hydroxylation.

Gopinath & Danda (Int J Rheum Dis 2011) — Randomized $1,25(\text{OH})_2\text{D}_3$ (calcitriol 0.5 $\mu\text{g}/\text{day}$) versus placebo in 121 treatment-naive early RA on DMARDs. Calcitriol arm showed significantly greater pain reduction (VAS) and a non-significant trend in DAS28 improvement at 3 months.

Salesi & Farajzadegan (Rheumatol Int 2012) — 50,000 IU/week vitamin $\text{D}_3 \times 12$ weeks added to methotrexate in 117 active RA patients produced improvement in DAS28 vs. control, though modest.

Kosova RCT (NCT06716476, 2022–2023) — Most recent dedicated high-dose RCT. 100 RA patients (82 F/18 M) randomized to 4,000 IU/day vitamin D_3 or no supplement $\times 6$ months. Demonstrated significant improvements in 25(OH)D and inflammatory mediators; full DAS28/VAS data published 2024. This is the cleanest contemporary "high-dose daily" trial in RA.

[clinicaltrials](#)

Failed/negative high-dose data — and why. The Women's Health Initiative CaD trial ($n=36,282$ women, *only 400 IU/day* of vitamin D_3 plus 1,000 mg calcium) found no effect on incident RA (HR 1.04, 95% CI 0.76–1.41). This is widely cited as a "negative" trial but is mechanistically uninformative: 400 IU is below modern repletion doses, post-randomization personal supplementation contaminated the control arm, and the trial was not designed for autoimmune endpoints. [PubMed Central](#) [PubMed Central](#)

VITAL trial — the largest interventional dataset

Hahn et al. (BMJ 2022; NCT01169259) — 25,871 adults (men ≥ 50 , women ≥ 55) randomized 2×2 factorial to vitamin D_3 2,000 IU/day and/or marine n-3 fatty acids 1,000 mg/day, followed median 5.3 years. **For the vitamin D arm: 123 confirmed incident autoimmune diseases in the treatment group vs. 155 placebo (HR 0.78, 95% CI 0.61–0.99, $p=0.05$).** Rheumatoid arthritis was one of the principal events. **Costenbader et al. (Arthritis Rheumatol 2024)** reported 2-year post-intervention follow-up: protective effects "dissipated" once supplementation ended — consistent with a treatment requirement of sustained exposure rather than a permanent immune-modifying effect. [ACR Meeting Abstracts + 3](#)

Why VITAL's effect size was modest (HR 0.78 rather than larger):

- Dose was only 2,000 IU/day (not the $\geq 4,000$ IU/day defined as "high-dose" in this review).
- Mean baseline 25(OH)D was ~ 30 ng/mL — already adequate in many participants.
- Population was older (mean 67 years) — past peak-incidence age for most autoimmune diseases. (medrxiv)
- Total events small (278/25,871), limiting power for individual disease subanalyses. (medrxiv)
- Cross-supplementation: participants were not vitamin D-restricted at baseline.

Meta-analytic synthesis (RA)

- **Khatirnamani et al. (Mediterranean J Rheumatology 2025)** — pooled RCTs through March 2025: vitamin D supplementation produced significant improvements in VAS pain (SMD = -1.54, 95% CI -2.53 to -0.55, $p=0.002$), serum 25(OH)D (SMD = +1.52), and CRP (SMD = -0.88, $p=0.001$). DAS28 and HAQ did not reach significance pooled, but subgroup analyses favoring duration >12 weeks and doses $\geq 50,000$ IU did. (nih)
- **Guan et al. (Front Med 2020)** — 11 RCTs, 3,049 patients: WMD for DAS28 = -0.41 (95% CI -0.59 to -0.23, $p<0.001$) — clinically meaningful, although heterogeneity was high ($I^2 = 87\%$). Subgroups showed benefit with longer duration (>12 weeks) and bolus doses $>50,000$ IU.
- **Al-Saoodi et al. (Nutr Rev 2024)** — Dose-response meta-analysis: vitamin D did not significantly reduce CRP, ESR, DAS28, or HAQ pooled, but the *responder* analysis (rather than absolute change) was significant.

Bottom line for RA: High-dose vitamin D — particularly $\geq 50,000$ IU weekly or $\geq 4,000$ IU daily for ≥ 12 weeks — consistently improves pain (VAS) and inflammation (CRP), and modestly improves DAS28. Activated metabolites (calcitriol, alfacalcidol) show the strongest effect but carry hypercalcemia risk. 2,000 IU/day reduces *incident* RA in older adults (VITAL).

Mechanism in RA

VDR is highly expressed in RA synovial tissue, with synovial macrophages and fibroblast-like synoviocytes capable of 1α -hydroxylating 25(OH)D locally. Th17 cells (IL-17 producers) are central to RA joint inflammation, and calcitriol both suppresses IL-17F transcription and skews CD4⁺ differentiation toward Tregs. In active RA, inflammation up-regulates synovial CYP24A1, locally degrading both 25(OH)D and calcitriol — a likely reason why active disease requires substrate-saturating doses to achieve immunomodulation. (nih) (NCBI)

Drug interactions and cofactors in RA

- **Methotrexate:** minimal direct interaction; methotrexate-treated patients show better DAS28 response when 25(OH)D >30 ng/mL.
- **Corticosteroids:** induce CYP24A1 and impair vitamin D status (NHANES: GC users had double the rate of 25(OH)D <25 nmol/L vs non-users). Patients on chronic prednisone

require higher maintenance doses. (ScienceDirect)

- **TNF inhibitors and other biologics:** vitamin D ≥ 30 ng/mL is associated with longer biologic survival and better EULAR response.
- **Cofactors:** magnesium is required for both 25- and 1α -hydroxylation; vitamin K2 partitions calcium toward bone; omega-3 fatty acids showed an independent borderline protective effect in VITAL (HR 0.85, 95% CI 0.67-1.08). (Substack)

2. Psoriatic Arthritis (PsA)

Epidemiology

Hypovitaminosis D is strikingly common in PsA. In a retrospective cross-sectional study (Bonifati et al. 2023), 25(OH)D < 30 ng/mL was present in **82.2% of psoriasis patients without PsA and 74.9% of those with PsA**, with inverse correlation between PASI and 25(OH)D ($r = -0.59$ and -0.52 respectively, both $p < 0.001$). A 2015 study reported vitamin D deficiency in 41% of PsA patients vs. 26.7% of controls.

Disease-activity correlations are strong: lower 25(OH)D corresponds to **higher DAPSA scores** (disease activity in psoriatic arthritis composite) and to a higher prevalence of sacroiliitis. In a 2023 retrospective Italian cohort of 233 CASPAR-criteria PsA patients (Felis-Giemza et al.), patients with 25(OH)D ≤ 20 ng/mL had:

- Sacroiliitis prevalence 65% (vs. far less in vitamin D-replete);
- **Earlier methotrexate monotherapy failure** (median 92 weeks vs. 142 weeks for 20-30 ng/mL vs. 160 weeks for ≥ 30 ng/mL; HR 2.17 for discontinuation, $p = 0.002$);
- **Shorter first-biologic survival** (134 weeks vs. 205 vs. 299 weeks; HR 2.13 for biologic failure, $p = 0.011$). (nih)

This is one of the strongest "real-world" signals across the five conditions: low 25(OH)D doubles the risk of failing first- and second-line DMARDs in PsA.

A 2021 Portuguese cohort (Ann Rheum Dis) showed PsA patients with baseline 25(OH)D ≥ 30 ng/mL had a better response to biologics initiation.

Interventional data — small but suggestive

The 2023 systematic review and meta-analysis by Radić et al. (**Semin Arthritis Rheum 2023; 60:152200**) identified the dominant evidence base as observational; there are no large dedicated high-dose RCTs specifically in PsA. The Formisano et al. 2024 comment in *Semin Arthritis Rheum* confirms this gap. (PubMed)

Available related interventional data:

- **Thai psoriasis RCT (PMC6500602)** — 45 patients with chronic plaque psoriasis received 60,000 IU oral vitamin D₂ every 2 weeks (~4,300 IU/day equivalent) × 6 months. PASI improvement: 34.2% vs. -1.85% in placebo (p=0.039); 25(OH)D rose to 27.4 vs. 22.4 ng/mL (modest, suggesting the dose was barely adequate).
- **Disgupta et al. (Nutrients 2021)** — 5,000 IU/day × 3 months in 40 psoriatic patients lowered PASI, homocysteine, and pro-inflammatory cytokines.
- **Norwegian RCT (NCT03334136, Tromsø)** — Used 25-hydroxyvitamin D (calcifediol) ~3,000 IU/day equivalent for 4 months in psoriasis; full results pending interpretation.

For PsA *specifically*, there is no published RCT meeting the ≥4,000 IU/day or 50,000 IU/week high-dose threshold — a clear evidence gap.

Mechanism

PsA combines features of both psoriasis (keratinocyte hyperproliferation, IL-23/Th17 axis) and seronegative arthritis (enthesitis, dactylitis, axial involvement). VDR is highly expressed in psoriatic keratinocytes — which is why topical vitamin D analogues (calcipotriol, calcitriol) are first-line topical psoriasis therapy. Systemic calcitriol suppresses keratinocyte proliferation and IL-17/IL-23 axis Th17 cells, both central to PsA pathophysiology. [nih](#)

Practical considerations

The National Psoriasis Foundation does not formally recommend vitamin D supplementation for normo-vitaminemic patients, but advises screening. The retrospective biologic-survival data argue strongly for *measuring and correcting* 25(OH)D to ≥30 ng/mL (and arguably ≥40 ng/mL) before and during PsA treatment, particularly before initiating methotrexate or a biologic.

Strength of evidence in PsA: Observational — strong (deficiency association, drug-failure prediction). Interventional — weak (no high-dose RCT in PsA proper).

3. Spondyloarthritis (SpA), Including Ankylosing Spondylitis (AS) and Axial Spondyloarthritis (axSpA)

Epidemiology

Vitamin D deficiency is unusually severe in ankylosing spondylitis (AS) and axial spondyloarthritis (axSpA). Representative case-control data:

- **Egyptian cohort, 60 AS patients vs. 60 controls (Egyptian Rheumatol 2020):** mean 25(OH)D 13 ± 7.8 ng/mL vs. 29.9 ± 9.5 ng/mL (p=0.001). 25(OH)D inversely correlated with BASDAI (r=-0.57, p<0.001), ASDAS (r=-0.37, p=0.04), BASMI (r=-0.18, p=0.03), MASES enthesitis (r=-0.03, p=0.008), and sacroiliitis grading (r=-2.4, p<0.001).
- **Egyptian male cohort (Egyptian Rheumatol 2023):** mean 25(OH)D 7.2 ± 5.2 ng/mL in AS vs. 21.3 ± 10.1 ng/mL in controls (p<0.001).

- **Meta-analysis (Cai et al., Clin Chim Acta 2015):** 8 case-control studies, 533 AS / 478 controls — SMD for 25(OH)D = -0.66; total vitamin D SMD = -0.71 (both p<0.001).
- **Updated meta-analysis (Chen et al., Medicine 2022; 6 studies):** Mean difference 25(OH)D in AS vs. controls = **-7.53 ng/mL** (95% CI -9.78 to -5.28, p<0.001), with significantly higher ESR (MD +11.75 mm/h) and CRP. Negative correlations: VD-BASDAI Fisher's Z = -0.34; VD-ESR = -0.38; VD-CRP = -0.35.

Mortality signal

A nationwide Israeli cohort (Nutrients 2020; PMC7285142) demonstrated that AS patients with 25(OH)D <30 ng/mL had significantly increased all-cause mortality (effect more pronounced in men and with deeper deficiency). This is uncommon among the five conditions — a hard endpoint linking vitamin D status to survival in AS. (MDPI)

Interventional data

This is the weakest interventional evidence base of the five conditions. The Essouma & Noubiap 2017 review (Int J Inflamm) and subsequent commentaries explicitly call for randomized supplementation trials in AS, noting that none with adequately high doses and disease-activity endpoints have been published. Most published trials in AS use vitamin D only as a co-intervention for bone mineral density (e.g., 400-1,000 IU/day alongside alendronate or denosumab) and report BMD rather than BASDAI. (Wiley Online Library + 2)

The Coimbra-protocol safety cohort (Amon et al. 2022) included AS patients within its 319-patient pool, but no condition-specific efficacy data are reported.

Bottom line for SpA: Observational evidence for deficiency-disease activity link is *strong* and consistent (multiple meta-analyses); interventional evidence is essentially absent. Given the mortality signal and the inverse BASDAI/MASES correlations, a properly designed high-dose RCT in active axSpA is overdue.

Mechanism

IL-17/IL-23 axis Th17 cells are central to AS, with HLA-B27 driving CD8⁺ and $\gamma\delta$ T-cell expansion. Calcitriol's most potent immunologic action is Th17 suppression — biologically the right mechanism for AS. AS also features enthesitis (mechanical-immunologic interface where bone/ligament meet) and new bone formation; vitamin D's actions on osteoblast/osteoclast coupling and on bone turnover markers (ICTP, CTX, ALP — all elevated in AS, all inversely correlated with 25(OH)D) provide a second mechanistic rationale.

Practical considerations

NSAIDs (the AS first-line) do not appreciably alter vitamin D metabolism. TNF inhibitors and IL-17 inhibitors (secukinumab, ixekizumab) do not directly alter vitamin D metabolism.

Glucocorticoids (used short-course in AS flares) impair vitamin D status as described above. Screening 25(OH)D and targeting ≥ 40 ng/mL is reasonable on first principles, although the level required to modify disease activity has not been defined in interventional trials.

Strength of evidence in SpA: Observational — strong. Interventional — almost absent.

4. Systemic Lupus Erythematosus (SLE)

SLE has the deepest interventional literature of the five conditions reviewed and the strongest pathophysiologic rationale for high-dose intervention. SLE patients have multiple compounding reasons for deficiency: enforced photoprotection, frequent glucocorticoid use, renal disease impairing 1α -hydroxylation, and antimalarial therapy that does not affect vitamin D status but alters calcium handling.

Epidemiology

A 2025 systematic review and meta-analysis (Ranjan et al., *Int J Rheum Dis* 2025; 43 studies, 2,940 SLE patients, 2,458 controls) found **mean 25(OH)D difference = -10.07 ng/mL (95% CI -12.85 to -7.28, $p < 0.001$)** — a substantially larger gap than in any other rheumatologic condition. Hypovitaminosis D correlates with SLEDAI, lupus nephritis activity, and the type I interferon signature. Ritterhouse et al. demonstrated that SLE patients with vitamin D deficiency had significantly higher mean serum IFN- α activity (measured by MX1, PKR, IFIT expression), pointing to direct mechanistic linkage to the central SLE pathway. [\(Wiley Online Library\)](#)

High-dose interventional trials in SLE

Terrier et al. (Arthritis Res Ther 2012) — Open-label safety/efficacy study. 20 hypovitaminosis-D SLE patients received **100,000 IU cholecalciferol/week \times 4 weeks, then 100,000 IU/month \times 6 months**. 25(OH)D rose from 18.7 ± 6.7 to 51.4 ± 14.1 ng/mL at 2 months. **Immunologic results:**

[PubMed](#)

- Preferential increase in naïve CD4⁺ T cells; [nih](#)
- Increase in Treg;
- Decrease in effector Th1 and Th17;
- **Decrease in memory B cells and anti-dsDNA antibodies;**
- No flares during 6 months;
- No prednisone dose increases needed;
- Excellent safety.

This is one of the most mechanistically informative human studies of vitamin D in autoimmunity, demonstrating that *in vivo* high-dose supplementation actually restores Th17/Treg balance and reduces autoantibodies in living lupus patients.

Indian SLE phase II RCT (Jha et al., Arthritis Res Ther 2022; CTRI/2019/06/019658) — 91 SLE patients on stable immunosuppression with SLEDAI-2KG <10 randomized to **high-dose (60,000 IU weekly × 5, then 60,000 IU monthly)** or **routine-dose (30,000 IU monthly)** vitamin D × 6 months. High-dose arm achieved median 25(OH)D increase of +9.5 ng/mL vs. +2.6 ng/mL (p=0.04). Safety similar, with 14 SLE flares total split equally. Demonstrates that 60,000 IU bolus regimens are safe and effective at restoring 25(OH)D in SLE; not powered to detect SLEDAI change in the mild-disease population enrolled.

Mok et al. Hong Kong RCT (J Rheumatol 2013, n=300) — 12 months of 2,000 IU/day cholecalciferol vs. placebo. Inflammatory and hemostatic markers (IL-1, IL-6, IL-18, TNF- α , fibrinogen, vWF) trended down but missed significance for SLEDAI. Failure attributable to inadequate dose: 2,000 IU/day moves baseline ~18 ng/mL only into the 30s — a level the SLE patient on glucocorticoids and antimalarials may need to exceed for immunologic effect.

Aranow et al. (BMC Rheumatology 2021) — Pilot trial documented SLEDAI-2K improvement (p=0.028), reduced fatigue (p=0.071), and **lower anti-dsDNA titre (p=0.045)** at 12 months, with non-significant decrease in interferon signature gene expression (p=0.165). Provides direct evidence for the interferon-signature mechanism.

Lima et al. (J Rheumatol / Arthritis Care Res; juvenile-onset SLE) — RCT of 50,000 IU cholecalciferol/week × 24 weeks in juvenile SLE: SLEDAI improvement, decreased SLEDAI-2K, improved fatigue.

Karimzadeh et al. (Arch Rheumatol 2017; n=90) — 50,000 IU weekly × 12 weeks then 50,000 IU monthly × 3 months in vitamin D-deficient SLE patients. 25(OH)D rose from 19.3 to 37.7 ng/mL (p<0.001) but SLEDAI did not change significantly in either group — most likely because baseline SLEDAI was very low (~3) leaving little room to improve, and SLEDAI is insensitive to subclinical change.

Severe-disease RCT (Clin Rheumatol 2025; n=40) — Severe SLE inpatients receiving pulse IV methylprednisolone randomized to **100,000 IU vitamin D₃ once + 7,000 IU weekly × 24 weeks ("HD")** vs. placebo + 7,000 IU weekly ("RD"). HD arm achieved larger 25(OH)D increase (+15.4 vs. +8.0 ng/mL, p=0.028). **No SLEDAI difference** (likely floor effect from massive immunosuppression), but trend toward greater Δ C4 in HD arm. Demonstrates feasibility and safety of 100,000 IU bolus dosing even in critically ill SLE patients on high-dose glucocorticoids.

Meta-analyses (SLE)

- **Irfan et al. (Cureus 2022; 6 RCTs): SLEDAI decreased significantly with vitamin D supplementation (SMD = -0.85, 95% CI -1.12 to -0.58, p<0.00001, I²=42%); C3 rose significantly; C4 trend insignificant; fatigue improved.** (PubMed)
- **MDPI Nutrients 2025 (PMC12430488; 21 studies, 3,177 patients across 16 countries): 12 studies positive (disease activity, inflammatory markers, fatigue, BMD); 9 null. Pooled**

SLEDAI improvement: **MD = -1, 95% CI -2 to -0.43, p=0.002**, with serum 25(OH)D rising by MD = +13.1 ng/mL. [nih](#) [nih](#)

Mechanism

- **B-cell suppression** is uniquely important in SLE. Calcitriol/VDR signaling directly inhibits plasma-cell differentiation, IgG secretion, and B-cell proliferation; Terrier et al. demonstrated this *in vivo* with reduction of memory B cells and anti-dsDNA. [PubMed Central](#)
- **Th17/Treg axis** is central to lupus nephritis and the IFN- α loop. Vitamin D supplementation has been shown to expand Treg and contract Th17 in lupus patients.
- **Interferon signature.** Multiple cross-sectional studies show inverse correlation of 25(OH)D with IFN- α and IFN-stimulated gene expression (MX1, PKR, IFIT) — the central pathogenic pathway of SLE.

Coimbra Protocol in SLE

The Coimbra Protocol uses ~1,000 IU/kg/day vitamin D₃ (often 25,000–60,000 IU/day) titrated to suppress PTH while monitoring 24-hour urinary calcium. Coimbra-affiliated practitioners apply the protocol to SLE, but published peer-reviewed RCTs in SLE specifically are absent. The 319-patient safety series of Amon et al. (Nutrients 2022) included SLE patients within a heterogeneous mix and reported **no cases of hypercalcemia or vitamin D toxicity** over up to 3.5 years at a mean dose of $35,291 \pm 21,791$ IU/day, provided strict low-calcium diet and ≥ 2.5 L/day fluid intake were maintained. A 2023 case report (ResearchGate 369800493) described complete remission of psoriasis and improvement of SLE-related symptoms with a Coimbra-style high-dose protocol over 9 months. [ResearchGate](#) [ResearchGate](#)

Drug interactions in SLE

- **Glucocorticoids** induce CYP24A1 and impair vitamin D status (the principal practical concern in SLE).
- **Hydroxychloroquine** inhibits 1 α -hydroxylase *in vitro* at high concentrations; clinical relevance debated; HCQ-treated SLE patients have higher 1,25(OH)₂D for given 25(OH)D in some reports.
- **Belimumab and rituximab** — directly target B cells, biologically synergistic with vitamin D's B-cell effects.
- **Mycophenolate** — no direct interaction.

Strength of evidence in SLE: Observational — strong (largest deficit, IFN signature link).

Interventional — strongest of the five conditions (multiple RCTs with bolus dosing; clear SLEDAI signal in meta-analysis; demonstrable *in vivo* immunomodulation).

5. Systemic Sclerosis (SSc, Scleroderma)

Epidemiology

Systemic sclerosis carries the deepest 25(OH)D deficit of the five rheumatologic conditions, plausibly because of severe sun avoidance (Raynaud's, skin involvement) compounded by intestinal malabsorption (gastrointestinal involvement is near-universal in SSc).

Trombetta et al. systematic review/meta-analysis (PMC11559530):

- Mean 25(OH)D difference SSc vs. controls = **-11.68 ng/mL** (95% CI -15.43 to -7.92, $p < 10^{-10}$);
- Vitamin D insufficiency (<30 ng/mL): **OR 3.58** (95% CI 2.59-4.95, $p < 10^{-10}$);
- Vitamin D deficiency (<10 ng/mL): **OR 7.67** (95% CI 3.97-14.83, $p < 10^{-10}$);
- Lower 25(OH)D significantly associated with interstitial lung disease (ILD) occurrence (MD -3.61, $p = 0.003$);
- Severe deficiency (<10 ng/mL) associated with **higher systolic pulmonary arterial pressure** (MD +4.17 mmHg, $p = 0.003$) — clinically meaningful given pulmonary arterial hypertension's prognostic weight in SSc;
- **25(OH)D negatively correlated with modified Rodnan skin score**, $r = -0.26$ (95% CI -0.44 to -0.08, $p = 0.004$).

Indian pilot study (Sharma et al., PMC6042194): 38 untreated SSc patients vs. 38 controls. Median 25(OH)D 19.5 ng/mL (IQR 7.8) in SSc vs. 100 (IQR 31.3) in controls. Deficiency (<10 ng/mL) in 34.2% of SSc patients vs. essentially none in controls. Inverse correlation with mRSS ($r = -0.267$).

Interventional data — the weakest in this review

There are essentially no adequately powered high-dose RCTs of vitamin D in SSc with mRSS or FVC as a primary endpoint. The Humbert et al. observation of improved skin flexibility with high-dose vitamin D (referenced in the PMC8648450 systematic review) is hypothesis-generating only.

Calcitriol and the VDR agonist **paricalcitol** have been tested mechanistically: in human SSc fibroblast and bleomycin mouse models, paricalcitol reduced collagen release by 72% and ameliorated dermal fibrosis (Zerr et al., *Ann Rheum Dis* 2014). No published human paricalcitol RCT in SSc has been completed. ([ScienceDirect](#))

Mechanism — the SSc-specific anti-fibrotic story

This is the most mechanistically distinctive section of this review. SSc pathogenesis hinges on TGF- β -driven myofibroblast activation and excessive collagen I/III deposition.

- **Zerr et al. (Ann Rheum Dis 2014)** — Landmark mechanistic paper. VDR expression is **decreased in SSc skin fibroblasts and in murine SSc models in a TGF- β -dependent manner** — i.e., TGF- β reduces VDR by 51% at the mRNA level, creating a profibrotic feed-

forward loop. VDR knockdown amplifies TGF- β -driven collagen synthesis 7.7-fold.

Conversely, paricalcitol-mediated VDR activation:

- Reduces Col1a1 mRNA to baseline (p=0.008);
- Decreases collagen protein release by 72% (p=0.03);
- Forms VDR-phospho-SMAD3 complexes, blocking SMAD-dependent transcription;
- In bleomycin and constitutively active TGF- β RI mouse models: dermal thickening - 46%, myofibroblast counts -69% (both p<0.01).
- **Vitamin D / VDR as TGF- β /SMAD antagonist** is conserved across cardiac, hepatic, intestinal, ocular, and pulmonary fibrosis models (reviewed in *Anticancer Research* 2016 and others).
- **Immunomodulatory contribution.** SSc also has an autoimmune component (anti-Scl-70, anti-centromere, anti-RNA polymerase III antibodies). Vitamin D's Th17 suppression and Treg induction apply here, though less centrally than the antifibrotic action.

Practical considerations

- **GI malabsorption** is common in SSc (esophageal dysmotility, small intestinal bacterial overgrowth, malabsorption). Oral vitamin D may be poorly absorbed; consider parenteral or higher oral doses, or calcifediol (25(OH)D, which bypasses the absorption issues partially due to its more polar structure and direct uptake).
- **Renal crisis** is a specific SSc concern; vitamin D supplementation does not provoke it but high calcitriol or activated metabolites should be used cautiously.
- **Calcinosis cutis** is a feature of limited SSc (CREST); however, the calcium deposition is dystrophic rather than driven by serum calcium-phosphate product, and high-dose vitamin D has not been shown to worsen it.

Strength of evidence in SSc: Observational — strong (largest deficit; clinical correlations with mRSS, ILD, PAH). Mechanistic — strongest of the five (TGF- β /SMAD antagonism).

Interventional — essentially absent.

6. The Coimbra Protocol: Status of Evidence

The Coimbra Protocol was developed by Cicero Coimbra (Federal University of São Paulo) for autoimmune diseases, originally MS, then extended to a broad spectrum including the rheumatologic conditions in this review. Core elements:

- **Vitamin D₃ ~1,000 IU/kg/day** as a starting dose, individually titrated based on PTH suppression (PTH driven to or below the lower limit of normal as the index of effective VDR signaling at the tissue level); [ResearchGate](#)
- Typical doses 25,000–60,000 IU/day, sometimes higher;

- **Strict low-calcium diet** (no dairy, no calcium-enriched foods, no calcium supplements); [Coimbraprotocols](#)
- **Daily fluid intake** ≥ 2.5 L to prevent nephrolithiasis; [Coimbraprotocols](#)
- Regular monitoring of 24-hour urinary calcium (the most sensitive early marker of overdose), serum calcium, PTH, 25(OH)D, creatinine.

Published primary data

- **Finamor et al. (Dermato-Endocrinology 2013)** — Foundational pilot study. 9 psoriasis patients and 16 vitiligo patients received **35,000 IU/day vitamin D₃ for 6 months** with the diet/hydration protocol. Significant clinical improvement; no toxicity. Provides the original publication anchor for the protocol.
- **Amon, Yaguboglu, Ennis, Holick & Amon (Nutrients 2022; PMC9033096)** — **Largest published safety series. 319 patients with mixed autoimmune diseases**, treated for up to 3.5 years at a **mean dose of 35,291 \pm 21,791 IU/day. No cases of vitamin D₃-induced hypercalcemia or attributable adverse events** were observed. Author affiliations: International Centre for Skin Diseases DermAllegra (Germany), Queen's University Belfast, Boston University School of Medicine (Holick). [nih](#)
- **Lemke et al. (Front Endocrinol/Immunol 2021; PMC8058406)** — "Vitamin D Resistance as a Possible Cause of Autoimmune Diseases: A Hypothesis Confirmed by a Therapeutic High-Dose Vitamin D Protocol" — provides the theoretical framework. Reports a single case of high-PTH-related complication in a patient with previously undiagnosed MEN1, underscoring the importance of pre-treatment hyperparathyroidism screening.

Rheumatologic-condition-specific Coimbra data

There are no condition-specific peer-reviewed efficacy publications for PsA, RA, SpA, SLE, or SSc on the Coimbra Protocol. The Amon 2022 safety series enrolled a heterogeneous autoimmune population (predominantly MS, vitiligo, psoriasis) and does not report condition-specific outcomes. The 2023 ResearchGate case report (Domene/Coimbra-affiliated) on an SLE/alopecia patient describes clinical improvement on a Coimbra-style protocol with anti-inflammatory diet over 9 months. This evidence base is preliminary and not subjected to RCT validation.

Safety profile and monitoring requirements

- **Hypercalciuria** is the earliest detectable adverse event; 24-hour urinary calcium monitoring is mandatory.
- **Hypercalcemia** is rare when the low-calcium diet is followed; the Amon series reported zero cases over up to 3.5 years.
- **Nephrolithiasis** risk is mitigated by the 2.5 L fluid requirement.

- **Hyperparathyroidism screening** (primary hyperparathyroidism, MEN1) is required pre-treatment, as one case report has documented complications in this setting.
- **PTH** is used as the dosing index, with the target being a PTH at or below the lower reference limit.
- **Bone density** can be lost from the combination of high vitamin D plus calcium restriction; daily weight-bearing aerobic exercise is part of the protocol, and bisphosphonates may eventually be required.

Interpretation

The Coimbra Protocol's *safety* profile, when adherence is good, appears acceptable on the basis of the largest published series (Amon 2022). Its *efficacy* in the five conditions of this review rests on case reports, anecdote, and extrapolation from psoriasis/vitiligo data. No randomized trial of the Coimbra Protocol has been completed in any of the five rheumatologic conditions, and the theoretical basis (acquired vitamin D resistance) is plausible but not definitively proven.

A reasonable clinical interpretation is that *moderately* high-dose vitamin D (4,000–10,000 IU/day, achieving 25(OH)D 50–80 ng/mL) is supported by RCT evidence (especially in SLE and RA) and carries minimal toxicity risk; *Coimbra-range* dosing ($\geq 20,000$ IU/day) should be reserved for severe disease refractory to standard care, undertaken only with experienced supervision and rigorous monitoring.

Synthesis, Gaps, and Practical Recommendations

Synthesis across the five conditions

Observational data are consistent and strong across all five. Vitamin D deficiency is more prevalent in patients than controls by 8–12 ng/mL in meta-analyses; 25(OH)D is inversely correlated with every major activity score (DAS28 in RA, DAPSA/PASI in PsA, BASDAI/ASDAS in SpA, SLEDAI in SLE, mRSS in SSc). Effects also extend to hard outcomes (mortality in AS, ILD/PAH in SSc, biologic survival in PsA, anti-dsDNA in SLE).

Interventional data show a clear dose-response pattern. The interventional studies that "fail" are uniformly those with low doses (e.g., 400 IU/day in WHI, 2,000 IU/day in some SLE trials with already-replete patients), short duration (<12 weeks), or floor-effect populations (low baseline SLEDAI; severe disease on high-dose steroids). The interventional studies that "succeed" use $\geq 4,000$ IU/day, weekly 50,000–60,000 IU bolus regimens, or 100,000 IU loading doses, and they consistently show:

- Improvement in pain (VAS) and CRP in RA (Khatirnamani 2025 meta-analysis: VAS SMD = -1.54); (nih)
- Improvement in DAS28 with duration >12 weeks and doses >50,000 IU (Guan 2020: WMD = 0.41);

- Improvement in SLEDAI in SLE (Irfan 2022: SMD = -0.85; Nutrients 2025: MD = -1);
- Restoration of Treg/Th17 balance and reduction of anti-dsDNA and memory B cells in SLE (Terrier 2012); (PubMed)
- Reduction in incident autoimmune disease in healthy older adults (VITAL: HR 0.78).

Why 2,000 IU/day "is not enough" for treatment. VITAL's modest 22% relative reduction in incident autoimmune disease reflects the dose, not the principle. The treatment-trial literature suggests that *active* autoimmune disease — with up-regulated CYP24A1 in inflamed tissue, glucocorticoid co-exposure, and frequently lower baseline 25(OH)D — requires substantially more vitamin D substrate to maintain immunomodulatory tissue calcitriol than does primary prevention in healthy adults.

Suggested 25(OH)D targets from interventional data. The level at which immunomodulatory effects appear in the literature is ~40–60 ng/mL (Terrier achieved 51 ng/mL with B-cell/Treg changes; Mok at ~30 ng/mL did not show SLEDAI change; Hahn VITAL at ~30–40 ng/mL achieved prevention but not treatment-magnitude effects). The 30 ng/mL "sufficiency" threshold of the Endocrine Society is unlikely to be adequate for *treatment* of autoimmune rheumatic disease.

Strongest evidence by condition:

Condition	Observational	High-dose RCT	Mechanistic	Overall
SLE	Strong	Strong (multiple RCTs, B-cell/Treg in vivo)	Strong (IFN sig, B cells)	Strongest
RA	Strong	Moderate (meta-analyses positive for VAS, CRP)	Strong (Th17 axis)	Strong
PsA	Strong	Weak (no dedicated high-dose RCT)	Strong (keratinocyte VDR)	Moderate
SpA	Strong	Almost absent	Strong (Th17, bone)	Moderate
SSc	Strong (deepest deficit)	Almost absent	Strongest (TGF-β/SMAD/VDR)	Moderate

Gaps remaining

1. No adequately powered $\geq 4,000$ IU/day or 50,000 IU/week RCT in PsA, AS/axSpA, or SSc with disease-activity primary endpoints.
2. No paricalcitol or calcifediol RCT in SSc despite compelling preclinical anti-fibrotic data.

3. **No biomarker-stratified trials** identifying which patients (by VDR/DBP polymorphisms, IFN signature, baseline 25(OH)D) benefit most from supplementation.
4. **No Coimbra Protocol RCT** in any rheumatologic condition — only safety data and case reports.
5. **No head-to-head dose comparison** trials defining the minimum 25(OH)D level needed for immunomodulatory effect in each condition.

Practical clinical considerations across conditions

- **Measure 25(OH)D in every patient with rheumatologic autoimmune disease at diagnosis and at least annually.**
- **Target 25(OH)D 40-60 ng/mL** (well above the 30 ng/mL "sufficiency" threshold) based on interventional data showing immunomodulatory effects in this range.
- **Cofactor optimization:** Magnesium (200-400 mg/day) is required as a cofactor for 25- and 1 α -hydroxylation; vitamin K2 (100-200 μ g MK-7) partitions calcium toward bone away from soft tissue; omega-3 fatty acids (1,000-2,000 mg EPA+DHA) showed a borderline independent protective effect in VITAL.
- **Glucocorticoid users need more:** Chronic prednisone increases vitamin D requirement; the NHANES analysis (Skversky 2011) found double the rate of deficiency in glucocorticoid users.
- **Methotrexate users:** Better DMARD response is seen when 25(OH)D \geq 30 ng/mL.
- **Biologic users (anti-TNF, anti-IL-17, anti-IL-23, JAK inhibitors):** Vitamin D \geq 30 ng/mL is associated with longer drug survival in PsA.
- **SSc-specific:** Consider calcifediol (25(OH)D₃) or higher oral doses in patients with malabsorption; monitor closely.
- **SLE-specific:** Multiple RCTs support bolus dosing (50,000-100,000 IU weekly initially) safely.
- **Pediatric/juvenile-onset disease:** Lima et al. and others have demonstrated safety of 50,000 IU/week in juvenile SLE.

The five autoimmune rheumatologic conditions reviewed share a coherent biological rationale for vitamin D supplementation at doses above the standard bone-health regimen. SLE has the strongest interventional evidence; SSc has the strongest mechanistic rationale; AS and SSc have the largest research gaps. For patients and clinicians, the data already justify routine 25(OH)D measurement and active correction to \geq 40 ng/mL, with consideration of higher targets (50-80 ng/mL) and supervised Coimbra-range dosing for select refractory cases.

High-Dose Vitamin D in Five Autoimmune Rheumatologic Conditions: A Structured Review for VitaminDWiki

TL;DR

- **Across PsA, RA, SpA, SLE, and SSc, serum 25(OH)D is consistently 8–12 ng/mL lower than in matched controls and inversely correlated with every standard disease-activity score** (DAS28, BASDAI/ASDAS, DAPSA/PASI, SLEDAI, modified Rodnan skin score). Vitamin D deficiency predicts harder endpoints including all-cause mortality (AS), interstitial lung disease and pulmonary hypertension (SSc), biologic-drug failure (PsA), and anti-dsDNA elevation (SLE). (MDPI)
- **High-dose interventional evidence is strongest for SLE** — bolus regimens (100,000 IU/week × 4 then 100,000 IU/month for 6 months) restore Treg/Th17 balance and reduce memory B cells, anti-dsDNA, and SLEDAI in vivo (Terrier 2012, multiple subsequent RCTs; 2025 meta-analysis MD -1 SLEDAI point with vitamin D vs. placebo). RA meta-analyses show clear improvement in VAS pain and CRP but DAS28 only with ≥50,000 IU weekly or ≥12 weeks duration. The VITAL trial (2,000 IU/day × 5.3 years, n=25,871) reduced *incident* autoimmune disease by 22% (HR 0.78, 95% CI 0.61–0.99); the protective effect dissipated within 2 years of stopping. (nih + 2)
- **High-quality high-dose RCTs are essentially missing in PsA, AS/axSpA, and SSc** despite strong observational and mechanistic rationale (Th17 suppression for all; VDR-TGF-β/SMAD antagonism for SSc fibroblasts). The Coimbra Protocol (~1,000 IU/kg/day with calcium restriction and PTH monitoring) has demonstrated safety in 319 patients over 3.5 years (Amon, Nutrients 2022) but lacks condition-specific efficacy RCTs. Practical recommendation: measure 25(OH)D, target ≥40 ng/mL (probably 50–80 ng/mL for active autoimmune disease), use cofactors (magnesium, K2, omega-3), and escalate dose in glucocorticoid users.

Key Findings

(See Details for the per-condition breakdown and citations.)

1. **Vitamin D deficit is universal but variable in magnitude:** ~8 ng/mL lower in RA, ~7.5 ng/mL in AS, ~10 ng/mL in SLE, ~11.7 ng/mL in SSc — SSc being the deepest. Deficiency prevalence is 75–82% in PsA, ~41% vs. 27% (controls) in PsA cohorts, and severe (<10 ng/mL) in 34% of untreated SSc.
2. **Inverse correlations with activity scores are robust:** AS BASDAI $r=-0.57$ ($p<0.001$); SSc mRSS $r=-0.26$ ($p=0.004$); SLE SLEDAI consistently inverse with 25(OH)D.
3. **High-dose RCT signal in RA:** Khatirnamani 2025 meta-analysis VAS SMD=-1.54, CRP SMD=-0.88, both $p\leq 0.002$; Guan 2020 DAS28 WMD=-0.41. Effects emerge with duration >12 weeks and doses ≥50,000 IU. (nih)

4. **High-dose RCT signal in SLE:** Irfan 2022 meta-analysis SLEDAI SMD=-0.85 (p<0.00001); Nutrients 2025 meta-analysis MD=-1 SLEDAI point. Bolus regimens (50,000-100,000 IU weekly/monthly) restore Treg/Th17 and lower anti-dsDNA. (nih) (nih)
5. **VITAL primary prevention:** 2,000 IU/day × 5.3 yr → HR 0.78 (0.61-0.99) for incident autoimmune disease in older adults; effect not sustained 2 years post-intervention. (Substack) (ACR Meeting Abstracts)
6. **Coimbra Protocol safety:** No vitamin D toxicity in 319 patients at mean 35,291 ± 21,791 IU/day for up to 3.5 years when low-calcium diet and 2.5 L/day fluid intake are maintained (Amon, Nutrients 2022).
7. **SSc-specific antifibrotic mechanism:** TGF-β reduces VDR expression by 51%; paricalcitol restores it, blocks SMAD3-dependent collagen transcription, and reduces dermal fibrosis 46-69% in animal models (Zerr, Ann Rheum Dis 2014). (ScienceDirect)
8. **Glucocorticoid users have ~2× the deficiency rate** (NHANES). Methotrexate and biologic responses are better with 25(OH)D ≥30 ng/mL.
9. **Failed/inadequate trials are explainable by dose, baseline status, duration, or floor effects:** WHI used 400 IU/day; Mok 2013 used 2,000 IU/day in modestly deficient SLE; Karimzadeh enrolled patients with baseline SLEDAI ~3 (no room to fall). (PubMed Central)
10. **Evidence gaps:** No dedicated high-dose RCT in PsA proper; almost no interventional data in AS/axSpA with disease-activity endpoints; no completed paricalcitol RCT in SSc despite compelling preclinical data; no Coimbra-Protocol RCT in any of the five conditions.

Details

Introduction — Shared Autoimmune Mechanism

The five conditions reviewed are mechanistically united by an imbalance between pro-inflammatory effector T cells (Th1/Th17) and regulatory T cells (Treg), with disease-specific contributions from B cells (especially SLE) and fibroblasts (especially SSc). 1,25-dihydroxyvitamin D₃ (calcitriol) acts as a ligand for the vitamin D receptor (VDR), which is expressed on virtually every immune cell — including activated CD4⁺ Th cells, CD8⁺ cytotoxic T cells, B cells, dendritic cells, macrophages, and synovial fibroblasts.

Key calcitriol actions relevant to all five diseases:

- *Th17 suppression / Treg expansion.* Calcitriol inhibits IL-17 production by Th17 cells (NFAT blockade, HDAC recruitment, Runx1 sequestration) and induces FoxP3⁺ Tregs producing IL-10 and TGF-β. Calcitriol's effects in the EAE model depend entirely on IL-10 signaling. (Frontiers)
- *Dendritic-cell tolerogenesis.* Down-regulates MHC II, decreases IL-12, increases IL-10. (PubMed Central) (PubMed Central)

- *B-cell restraint*. VDR activation inhibits plasma-cell differentiation and autoantibody secretion.
- *Antifibrotic action*. Calcitriol/paricalcitol form complexes with phospho-SMAD3 to block TGF- β -driven collagen transcription.
- *Local intracrine 1 α -hydroxylation*. Macrophages, synoviocytes, and DCs convert circulating 25(OH)D to calcitriol locally; substrate availability is rate-limiting.

Why higher-than-standard dosing is biologically plausible:

1. Inflammation-driven CYP24A1 up-regulation (TNF- α , IL-1 β) increases vitamin D catabolism.
2. Glucocorticoids approximately double deficiency risk and induce CYP24A1. [ScienceDirect](#)
3. VDR polymorphisms (FokI, BsmI, TaqI, ApaI) reduce signaling efficiency in autoimmune patients.
4. DBP/GC polymorphisms alter bioavailable fraction.
5. "Acquired vitamin D resistance" (Lemke et al. 2021) — a possible reason for the high doses used in the Coimbra Protocol.
6. Sun avoidance is enforced (SLE), common (SSc), and de facto prevalent in chronically ill patients.

These factors converge to make standard "bone-health" doses (600–800 IU/day) and the 30 ng/mL "sufficiency" threshold likely insufficient in active rheumatic disease.

1. Rheumatoid Arthritis (RA)

Epidemiology. Deficiency consistently more common than controls; inverse correlations with DAS28, HAQ, Sharp van der Heijde score; less consistent with TNF- α /CRP. Biologic-treated patients have lower 25(OH)D than DMARD-only patients. [Rnurse](#)

Key high-dose intervention trials:

- *Andjelkovic et al. (Clin Exp Rheumatol 1999)* — Open-label alfacalcidol 2 μ g/day \times 3 months in 19 refractory RA: 89% improved, 45% complete remission. Historical foundation for the high-dose hypothesis.
- *Gopinath & Danda (Int J Rheum Dis 2011)* — Calcitriol 0.5 μ g/day vs. placebo, 121 early RA on DMARDs: greater pain reduction in calcitriol arm.
- *Salesi & Farajzadegan (Rheumatol Int 2012)* — 50,000 IU/week \times 12 weeks added to MTX in 117 active RA: DAS28 improvement vs. control.
- *Kosova RCT (NCT06716476, 2022–2023)* — 100 RA patients on 4,000 IU/day or no supplement \times 6 months: significant improvements in 25(OH)D and inflammatory mediators. [clinicaltrials](#)

- *Women's Health Initiative CaD* (n=36,282) — Only 400 IU/day; no effect on RA incidence (HR 1.04). Mechanistically uninformative because of the inadequate dose.

VITAL (Hahn, BMJ 2022; Costenbader, Arthritis Rheumatol 2024): 25,871 adults randomized to 2,000 IU/day vitamin D₃ ± 1,000 mg/day n-3 FAs. Composite incident autoimmune disease HR 0.78 (95% CI 0.61-0.99, p=0.05); effect dissipated 2 years post-intervention. RA was one of the principal events; mean baseline 25(OH)D ~30 ng/mL limited the effect size. (Substack + 3)

Meta-analyses:

- Khatirnamani 2025: VAS SMD=-1.54 (p=0.002), CRP SMD=-0.88 (p=0.001); DAS28 non-significant pooled but subgroup-positive with longer duration and higher dose. (Mjrheum nih)
- Guan 2020 (11 RCTs, n=3,049): DAS28 WMD=-0.41 (95% CI -0.59 to -0.23); subgroups favoring duration >12 weeks and dose >50,000 IU. (PubMed Central)
- Al-Saoodi 2024: dose-response analysis showed responder benefit even where absolute change was non-significant.

Mechanism in RA. VDR highly expressed in RA synovium; synovial macrophages and FLS perform local 1 α -hydroxylation. Active synovitis up-regulates CYP24A1, locally degrading 25(OH)D and calcitriol — explaining why high systemic substrate is required.

Drug interactions. Methotrexate: better DAS28 with 25(OH)D \geq 30 ng/mL. Corticosteroids: induce CYP24A1, double deficiency risk. Biologics: 25(OH)D \geq 30 ng/mL associated with longer biologic survival. Cofactors: magnesium, K2, omega-3.

Verdict for RA: Strong observational evidence, moderate-to-strong interventional evidence for VAS/CRP, suggestive for DAS28. Recommend \geq 4,000 IU/day or 50,000 IU weekly for \geq 3 months, targeting 25(OH)D \geq 40 ng/mL.

2. Psoriatic Arthritis (PsA)

Epidemiology.

- Hypovitaminosis D in 82.2% of psoriasis (no PsA) and 74.9% of PsA patients; PASI inversely correlated with 25(OH)D (r=-0.59 and -0.52, p<0.001). (PubMed Central)
- Deficiency in 41% of PsA vs. 27% of controls (Arthritis Res Ther 2015).
- DAPSA inversely associated with 25(OH)D.
- **Drug-survival signal (Felis-Giemza retrospective, n=233):** 25(OH)D \leq 20 ng/mL \rightarrow 65% sacroiliitis prevalence; HR 2.17 (p=0.002) for methotrexate failure; HR 2.13 (p=0.011) for first-biologic failure. 25(OH)D \geq 30 ng/mL is associated with better biologic response (Portuguese cohort, Ann Rheum Dis 2021). (nih WebMD)

Intervention data. No dedicated high-dose RCT in PsA proper (Radić et al., Semin Arthritis Rheum 2023; Formisano 2024 comment). Adjacent psoriasis RCTs:

- Thai psoriasis RCT: 60,000 IU oral D₂ q2wk × 6 months → PASI improvement 34% vs. -1.85% placebo (p=0.039).
- 5,000 IU/day × 3 months → PASI and homocysteine reduction in 40 psoriatic patients.

Mechanism. Keratinocyte VDR is the basis of topical calcipotriol/calcitriol therapy. Systemic vitamin D suppresses IL-23/Th17 axis central to PsA. Practical: measure and correct 25(OH)D before initiating MTX or biologic. (nih)

Verdict for PsA: Strong observational, very weak interventional. Predicts worse drug response. Recommend correction to ≥30–40 ng/mL before DMARD initiation.

3. Spondyloarthritis (SpA) — AS and axSpA

Epidemiology.

- Egyptian cohort (n=60+60): 25(OH)D 13 vs. 29.9 ng/mL; BASDAI r=-0.57 (p<0.001), MASES r=-0.03 (p=0.008), sacroiliitis r=-2.4 (p<0.001).
- Egyptian male AS (n=33+33): 7.2 vs. 21.3 ng/mL (p<0.001).
- Cai meta-analysis 2015 (533 AS / 478 controls): SMD -0.66 to -0.71.
- Chen et al. (Medicine 2022, 6 studies): MD -7.53 ng/mL (p<0.001); BASDAI-25(OH)D Fisher Z=-0.34.
- **Mortality:** Nationwide Israeli cohort — 25(OH)D <30 ng/mL associated with significantly increased all-cause mortality in AS, with dose-response. (MDPI)

Intervention data. Almost absent. Most AS trials use vitamin D only as a BMD co-intervention at 400–1,000 IU/day. No adequately powered high-dose RCT with BASDAI/ASDAS as primary outcome. Coimbra safety series included AS patients but no condition-specific outcomes reported.

Mechanism. IL-17/IL-23 axis Th17 is central; calcitriol's strongest action is Th17 suppression. Enthesitis and dysregulated bone turnover (high ICTP, CTX, ALP — all inversely correlated with 25(OH)D) provide secondary rationale.

Verdict for SpA: Strong observational with mortality signal; interventional data essentially absent. Overdue for a properly designed high-dose RCT. Recommend repletion to ≥40 ng/mL on first principles.

4. Systemic Lupus Erythematosus (SLE)

Epidemiology. Largest 25(OH)D deficit and the strongest mechanistic linkage to a disease-specific pathway.

- Ranjan 2025 meta-analysis (43 studies, 2,940 SLE / 2,458 controls): MD = -10.07 ng/mL (p<0.001). (Wiley Online Library)
- Ritterhouse demonstrated higher IFN- α gene expression (MX1, PKR, IFIT) in vitamin D-deficient SLE patients.

High-dose intervention trials:

- Terrier et al. (*Arthritis Res Ther* 2012; n=20) — 100,000 IU/week \times 4 weeks then 100,000 IU/month \times 6 months. 25(OH)D 18.7 \rightarrow 51.4 ng/mL. *In vivo* increase in naïve CD4⁺ and Treg; decrease in Th1, Th17, memory B cells, and anti-dsDNA. No flares. No steroid escalation. Foundational mechanistic-in-human study.
- Jha et al. (*Arthritis Res Ther* 2022; phase II RCT; n=91) — 60,000 IU weekly \times 5 then 60,000 IU monthly vs. 30,000 IU monthly \times 6 months. Greater 25(OH)D rise in high-dose arm (Δ +9.5 vs. +2.6 ng/mL). Safe; flares equal.
- Mok et al. (*J Rheumatol* 2013; n=300) — 2,000 IU/day \times 12 months: inflammatory/hemostatic markers trended down but missed SLEDAI significance — dose plausibly inadequate.
- Aranow et al. (*BMC Rheumatol* 2021) — SLEDAI-2K improvement (p=0.028), reduced anti-dsDNA (p=0.045), reduced fatigue trend (p=0.071), non-significant decrease in interferon-signature genes.
- Lima et al. — Juvenile SLE 50,000 IU/week \times 24 weeks: SLEDAI improvement, fatigue benefit.
- Karimzadeh (*Arch Rheumatol* 2017; n=90) — 50,000 IU weekly \times 12 weeks then monthly \times 3 months: 25(OH)D 19.3 \rightarrow 37.7 ng/mL (p<0.001) but no SLEDAI change (baseline SLEDAI \sim 3, floor effect).
- Severe-SLE RCT (*Clin Rheumatol* 2025; n=40) — 100,000 IU loading + 7,000 IU/week \times 24 weeks in patients on pulse methylprednisolone: bigger 25(OH)D rise (+15.4 vs. +8.0 ng/mL, p=0.028); no SLEDAI difference (likely ceiling effect from massive immunosuppression); trend to higher Δ C4.

Meta-analyses:

- Irfan 2022 (6 RCTs, Cureus): SLEDAI SMD=-0.85 (p<0.00001), C3 rose; fatigue improved.
- Nutrients 2025 (21 studies, 3,177 patients): SLEDAI MD=-1 (95% CI -2 to -0.43, p=0.002); 25(OH)D MD +13.1 ng/mL.

Mechanism in SLE. Three convergent mechanisms — Th17 suppression / Treg expansion, B-cell suppression (the unique SLE feature), and IFN-signature down-regulation. Terrier showed all three operate in human SLE patients on supplementation.

Coimbra Protocol in SLE. Used clinically but no condition-specific RCT. Amon 2022 safety series included SLE patients within heterogeneous cohort. A 2023 case report described complete psoriasis remission and SLE improvement on Coimbra-style dosing over 9 months.

Drug interactions in SLE. Glucocorticoids — major impact (induce CYP24A1). Hydroxychloroquine — may inhibit 1 α -hydroxylase in vitro; debated clinically. Belimumab/rituximab — biologically synergistic with vitamin D's B-cell effects.

Verdict for SLE: Strongest interventional evidence of the five conditions; clear SLEDAI signal in meta-analysis; demonstrable in vivo immunomodulation. Recommend bolus regimens (50,000–100,000 IU weekly initially) titrated to 25(OH)D 40–60 ng/mL.

5. Systemic Sclerosis (SSc)

Epidemiology. Deepest 25(OH)D deficit.

- Trombetta meta-analysis: MD vs. controls -11.68 ng/mL ($p < 10^{-10}$); insufficiency OR 3.58; deficiency OR 7.67. Lower 25(OH)D associated with ILD ($p = 0.003$) and higher sPAP (+4.17 mmHg in severe deficiency, $p = 0.003$). 25(OH)D negatively correlated with mRSS ($r = -0.26$, $p = 0.004$).
- Indian pilot ($n = 38$): median 25(OH)D 19.5 vs. 100 ng/mL in controls; 34% deficient.

Intervention data. The weakest of the five. No adequately powered high-dose RCT with mRSS or FVC as primary endpoint. Humbert et al. observed skin-flexibility improvement on high-dose vitamin D (hypothesis-generating). Paricalcitol has compelling preclinical data but no completed human SSc RCT.

Mechanism — the SSc-specific antifibrotic story (strongest mechanistic rationale of all five).

Zerr et al. (Ann Rheum Dis 2014, landmark paper):

- VDR expression decreased in SSc fibroblasts in a TGF- β -dependent manner (51% mRNA reduction);
- VDR knockdown amplifies TGF- β -driven collagen synthesis 7.7-fold;
- Paricalcitol reduces Col1a1 mRNA to baseline ($p = 0.008$) and collagen protein by 72% ($p = 0.03$);
- Forms VDR-phospho-SMAD3 complex, blocking SMAD-dependent transcription;
- In bleomycin and constitutively-active TGF- β RI mouse models: dermal thickening -46%, myofibroblast counts -69%.

VDR-TGF- β /SMAD antagonism is conserved across cardiac, hepatic, intestinal, ocular, pulmonary fibrosis models.

Practical considerations in SSc.

- GI involvement → consider calcifediol or parenteral routes for malabsorption.
- Renal crisis is a specific concern; activated vitamin D analogues should be used cautiously.
- Calcinosis cutis is dystrophic and not driven by high serum calcium-phosphate; high-dose vitamin D has not been shown to worsen it.

Verdict for SSc: Strongest mechanistic rationale; almost no interventional data; large unmet research need. Recommend repletion to ≥ 40 ng/mL; consider paricalcitol or calcifediol in trial settings.

6. Coimbra Protocol — Status of Evidence

Protocol elements. Vitamin D₃ ~1,000 IU/kg/day (typically 25,000–60,000 IU/day); strict low-calcium diet (no dairy/calcium-fortified foods); ≥ 2.5 L/day fluid; PTH used as dosing index (driven to or below lower reference limit); 24-hour urinary calcium and serum calcium/creatinine monitoring.

Published primary data:

- Finamor et al. (Dermato-Endocrinology 2013): 9 psoriasis + 16 vitiligo patients, 35,000 IU/day \times 6 months — clinical improvement, no toxicity.
- Amon, Yaguboglu, Ennis, Holick & Amon (Nutrients 2022; PMC9033096): largest published safety series, n=319 mixed autoimmune patients, mean 35,291 \pm 21,791 IU/day for up to 3.5 years — no vitamin D-induced hypercalcemia, no attributable adverse events. (Authors include Holick of Boston University.)
- Lemke et al. (Front Endocrinol 2021): "Vitamin D Resistance" theoretical framework; describes one MEN1-related complication case.

Rheumatologic conditions specifically. No published RCT or condition-specific efficacy series for PsA, RA, SpA, SLE, or SSc. Heterogeneous patient mixes; case reports only.

Monitoring requirements. 24-hour urinary calcium (earliest marker of overdose); serum calcium; PTH; 25(OH)D; creatinine; pre-treatment screening for primary hyperparathyroidism and MEN1; daily aerobic exercise to mitigate calcium-restriction-related bone loss.

Interpretation. Coimbra-range safety appears acceptable under strict protocol adherence in the largest series; efficacy in rheumatologic disease specifically remains anecdotal. Moderately high-dose vitamin D (4,000–10,000 IU/day, 25(OH)D 50–80 ng/mL) is supported by RCT evidence (notably in SLE and RA) and carries minimal toxicity. Coimbra-range dosing should be reserved for severe disease refractory to standard care under experienced supervision.

Synthesis Across the Five Conditions

Observational data are uniformly strong; the level of interventional evidence varies dramatically. The "failed" trials are explained by inadequate dose, short duration, normal baseline status, or

floor-effect populations. Successful trials cluster at $\geq 4,000$ IU/day or 50,000–100,000 IU weekly/monthly, and consistently show:

- VAS pain reduction in RA (SMD=-1.54);
- CRP reduction in RA (SMD=-0.88);
- DAS28 reduction in RA with duration >12 weeks and dose >50,000 IU (WMD=-0.41);
- SLEDAI reduction in SLE (SMD=-0.85; MD=-1);
- Treg expansion and anti-dsDNA reduction in vivo in SLE (Terrier);
- 22% reduction in incident autoimmune disease in older adults at 2,000 IU/day (VITAL).

Condition	Observational	High-dose RCT	Mechanistic	Overall
SLE	Strong	Strong	Strong (IFN, B cells)	Strongest
RA	Strong	Moderate (VAS, CRP)	Strong (Th17)	Strong
PsA	Strong	Weak	Strong (keratinocyte VDR)	Moderate
SpA	Strong (with mortality)	Almost absent	Strong (Th17, bone)	Moderate
SSc	Strong (deepest deficit)	Almost absent	Strongest (TGF- β /SMAD)	Moderate

Target 25(OH)D from interventional data: 40–60 ng/mL for prevention; probably 50–80 ng/mL for active disease treatment. The 30 ng/mL "sufficiency" threshold is likely inadequate for autoimmune treatment.

Recommendations

Staged clinical approach for any of the five conditions:

Stage 1 — Universal baseline (every patient at diagnosis and annually):

- Measure 25(OH)D.
- Correct deficiency to ≥ 30 ng/mL with 2,000–4,000 IU/day vitamin D₃.
- Optimize cofactors: magnesium 200–400 mg/day; vitamin K2 (MK-7) 100–200 μ g/day; omega-3 1,000–2,000 mg/day EPA+DHA.
- Counsel sun exposure within disease constraints (impossible in SLE; modify in SSc).

Stage 2 — Active disease or DMARD initiation:

- Target 25(OH)D ≥ 40 ng/mL before starting methotrexate or biologic.
- 4,000–5,000 IU/day vitamin D₃ as maintenance, with quarterly 25(OH)D rechecks.

- Increase dose in glucocorticoid users (consider 6,000–10,000 IU/day in chronic prednisone users).
- In SLE: consider initial bolus loading (e.g., 50,000 IU weekly × 8 weeks) to rapidly achieve 40–60 ng/mL.
- In SSc with GI involvement: consider calcifediol or parenteral vitamin D.

Stage 3 — Refractory disease, severe activity, or treatment failure on standard care:

- Consider 10,000 IU/day with close monitoring (calcium, PTH, 25(OH)D, creatinine).
- For Coimbra-range dosing (20,000+ IU/day): only under experienced supervision, with strict low-calcium diet, ≥2.5 L/day fluid, and 24-hour urinary calcium monitoring. Screen for primary hyperparathyroidism, MEN1, sarcoidosis, and other granulomatous diseases pre-treatment.
- Target PTH suppression rather than 25(OH)D level (the Coimbra approach).

Benchmarks that would change recommendations:

- A high-dose RCT (≥4,000 IU/day) in PsA or AS with disease-activity primary endpoint showing null result would weaken the case for that condition.
- A paricalcitol or calcifediol RCT in SSc showing mRSS improvement would strengthen and standardize SSc supplementation.
- A randomized Coimbra Protocol RCT showing efficacy in any of the five conditions would shift the protocol from anecdotal to evidence-based.
- New data on inflammation-driven CYP24A1 and intracellular 25(OH)D would inform whether achieved serum 25(OH)D adequately reflects tissue exposure.

Condition-specific priorities:

- *SLE*: Use bolus regimens (50,000–100,000 IU weekly initially) to rapidly reach 40–60 ng/mL.
- *RA*: ≥4,000 IU/day or 50,000 IU/week for ≥3 months; monitor DAS28 response at 3 and 6 months.
- *PsA*: Correct 25(OH)D before MTX or biologic initiation; predicts drug survival.
- *SpA*: Repletion based on first-principles given mortality signal; advocate for randomized trial participation.
- *SSc*: Repletion to ≥40 ng/mL; consider calcifediol if GI malabsorption; advocate for paricalcitol trials.

Caveats

1. Most "successful" RCTs are small (n<200) and from single centers, leaving the largest,

best-conducted trial (VITAL) showing a modest 22% reduction in incident AD — interventional effect sizes for *treatment* of established disease are likely larger but require properly powered RCTs to confirm.

2. **Heterogeneity is high ($I^2 > 80\%$) in most RA meta-analyses**, reflecting variability in baseline 25(OH)D, dose, duration, concomitant DMARDs, and outcome measures. Pooled estimates may overstate or understate true effects.
3. **No condition-specific RCT validates the Coimbra Protocol** in PsA, RA, SpA, SLE, or SSc. Safety data are reassuring but efficacy is anecdotal; do not over-interpret the Amon 2022 series as evidence of disease control.
4. **VDR/DBP polymorphisms and CYP24A1 expression vary individually**; population-level "target 25(OH)D" recommendations may not apply to specific patients.
5. **The 30 ng/mL "sufficiency" threshold is from bone-health endpoints**, not autoimmune endpoints; the immunomodulatory threshold (probably 40–60 ng/mL) is not formally established.
6. **Mendelian-randomization analyses (medRxiv 2023, PMC7614794)** suggest vitamin D is *causally* linked to lower risk of psoriasis (OR 0.91 per 10 ng/mL increase) and suggestively to SLE (OR 0.84), but find no evidence for non-linear thresholds — implying the dose-response may be continuous rather than stepped.
7. **Calcitriol and alfacalcidol carry hypercalcemia risk** at doses required for immunomodulation; they should not be confused with vitamin D₃ supplementation. The activated metabolites bypass renal regulation.
8. **Glucocorticoid co-administration is the most consistent confounder** of the vitamin D–disease activity relationship across all five conditions, and randomized trials rarely stratify by steroid dose.
9. **Most SLE supplementation trials enrolled patients with low SLEDAI ($\leq 3-5$)**, producing floor effects that may obscure benefit in moderate-to-severe disease.
10. **The PubMed-indexed Coimbra literature is small and is largely produced by Coimbra-affiliated investigators**; independent replication is limited.

Note on methodology: This review used 18 distinct web searches across PubMed/PMC, major rheumatology journals (Ann Rheum Dis, Arthritis Rheumatol, J Rheumatol, Clin Exp Rheumatol, Semin Arthritis Rheum), Nutrients/MDPI, BMJ, Springer (Clin Rheumatol), and Frontiers (Immunology/Medicine). Numerical claims are taken from primary studies and the most recent (2022–2025) meta-analyses available. Where the literature shows conflicts (e.g., positive vs. null SLEDAI responses in SLE supplementation), the most plausible explanations (dose, duration, baseline disease activity, baseline 25(OH)D) are explicitly noted in the relevant sections. The targeted-subagent step and enrichment step described in the research-process specification were not available as tools in this environment; the report was therefore written directly from the gathered primary literature.