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Vitamin D and Advanced Therapy Medicinal Products: A Scoping Review

Rima Melati [1*], Ineke Winda Ferianasari [2]
[1,2] President University, Indonesia
[1]rima_melatidr@yahoo.co.id*, [2]inekewfs@gmail.com

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ABSTRACT

Objectives: This scoping review maps the existing literature on the relationship between Vitamin D (VD) signaling and Advanced Therapy Medicinal Products (ATMPs), including cell-based therapies, gene therapies, and tissue-engineered constructs. It aims to synthesize current evidence on mechanistic links, translational relevance, and key research gaps.. Methods: A systematic search was conducted in PubMed, Scopus, and Web of Science for peer-reviewed studies published from inception through February 2025. Inclusion criteria required original or review articles indexed in Q1 journals examining VD or its receptor (VDR) in the context of ATMP modalities. Grey literature and predatory publishers were excluded. Study selection followed PRISMA-ScR guidelines, and 87 studies were included after full-text screening.. Key Findings: The literature clusters into four domains: (i) hematopoietic stem cell transplantation (HSCT), where VD deficiency correlates with increased graft-versus-host disease risk (HR 1.75, 95% CI 0.72–4.26) and reduced overall survival; (ii) mesenchymal stem cell (MSC) osteogenic differentiation, where 25(OH)D_3 at 250–500 nM robustly induces osteogenesis via VDR-mediated transcription and mineral deposition; (iii) CAR-T cell therapy, where emerging data suggest VD deficiency is associated with inferior progression-free survival (HR 2.53, 95% CI 1.14–5.66) in relapsed/refractory multiple myeloma; and (iv) tissue engineering, where VD_3-loaded scaffolds enhance osteoblast differentiation and neovascularization. No direct studies were identified linking VD to in vivo gene therapy vectors. Research Gaps: Prospective clinical trials assessing VD supplementation in ATMP recipients are lacking. The mechanistic role of VD in CAR-T cell fitness, stem cell homing, and graft-versus-tumor immunity remains poorly characterized. Standardized thresholds for VD sufficiency in ATMP contexts are absent. The potential for VD to modulate gene therapy vector immunogenicity is unexplored. Conclusions: VD represents a promising, low-cost adjunctive agent for ATMP optimization. Current evidence supports its potential roles in immune regulation, osteogenic differentiation, and stem cell maintenance, but dedicated clinical trials are needed to establish evidence-based supplementation protocols.

INTRODUCTION

Advanced Therapy Medicinal Products (ATMPs) represent a transformative class of therapies encompassing cell-based interventions (e.g., mesenchymal stromal cells, CAR-T cells), gene therapies (viral and non-viral vectors), and tissue-engineered constructs. Despite remarkable clinical successes particularly in hematological malignancies with chimeric antigen receptor (CAR)-T cell therapy and in monogenic disorders with adeno-associated virus (AAV)-mediated gene replacement significant challenges remain. These include limited in vivo persistence of transplanted cells, variable engraftment efficiency, immune-mediated rejection, and suboptimal functional integration of engineered tissues.

Vitamin D (VD), a secosteroid hormone with canonical roles in calcium and phosphate homeostasis, has emerged as a pleiotropic regulator of cell fate, immune function, and tissue repair. The active metabolite 1α,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] binds the nuclear vitamin D receptor (VDR), a ligand-activated transcription factor expressed in virtually all nucleated cells, including hematopoietic stem cells, T and B lymphocytes, dendritic cells, mesenchymal stromal cells, osteoblasts,

and epithelial stem cells. VDR signaling regulates the expression of hundreds of genes involved in proliferation, differentiation, apoptosis, and immune polarization.

At least four mechanistic axes link VD biology to ATMP efficacy:

1. Immune modulation. VD promotes a tolerogenic immune phenotype by inhibiting dendritic cell maturation (downregulating CD40, CD80, CD86), suppressing Th1/Th17 cytokine production (IFN-γ, IL-17), and expanding regulatory T cell (Treg) populations ($Foxp3^{+}CD25^{+}$). This is particularly relevant for allogeneic cell therapies where graft-versus-host disease (GVHD) remains a major barrier.
2. Stem cell maintenance and differentiation. VDR is required for epidermal stem cell self-renewal, migration, and differentiation during wound repair. In mesenchymal stem cells (MSCs), $25(OH)D_3$ induces osteogenic differentiation through upregulation of alkaline phosphatase (ALPL), osteopontin (SPP1), and osteocalcin (BGLAP), with superior mineralization compared to $1,25(OH)_2D_3$.
3. Hematopoietic support. VD stimulates $CD34^{+}$ hematopoietic stem cell proliferation and monocytic commitment. VD deficiency is associated with impaired neutrophil recovery and inferior survival following allogeneic hematopoietic stem cell transplantation (HSCT).
4. Tissue integration and angiogenesis. VD_3 enhances neovascularization in tissue-engineered constructs by promoting osteoblast-endothelial cell crosstalk, and when incorporated into scaffolds, it improves osteoblast attachment, proliferation, and alkaline phosphatase activity.

Although these biological effects have been investigated in diverse biomedical contexts, their relevance across distinct ATMP modalities has not been comprehensively synthesized. Importantly, VD may influence different therapeutic platforms through modality-specific mechanisms: enhancing persistence, immunoregulation, and functional potency in cell-based therapies; modulating transgene expression, vector performance, and host immune responses in gene therapy; and improving vascularization, scaffold integration, and tissue regeneration in tissue-engineered products. However, evidence regarding these modality-specific roles remains fragmented across disciplines and has not been systematically evaluated within the ATMP framework.

Despite growing interest, the relationship between VD and ATMPs has not been systematically mapped. This scoping review aims to (i) characterize the extent, range, and nature of the evidence linking VD to ATMP modalities; (ii) identify mechanistic pathways with translational potential; and (iii) highlight critical knowledge gaps requiring prospective investigation.

RESEARCH METHODS

This scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines (Tricco et al., 2018). A protocol was registered in the Open Science Framework (osf.io/xxxx). The review process was designed to ensure transparency, reproducibility, and consistency across all stages, including literature identification, screening, eligibility assessment, data charting, and synthesis.

Search Strategy

A systematic literature search was performed in PubMed, Scopus, and Web of Science Core Collection from database inception through February 28, 2025. The search strategy combined controlled vocabulary (MeSH, Emtree) and free-text terms for two conceptual domains: (i) Vitamin D (including "vitamin D," "calcitriol," "25-hydroxyvitamin D_3," "vitamin D receptor," "VDR"); and (ii) ATMPs (including "advanced therapy medicinal products," "cell therapy," "gene therapy," "tissue engineering," "stem cell transplantation," "CAR-T cell," "chimeric antigen receptor," "mesenchymal stem cell," "hematopoietic stem cell," "viral vector," "AAV," "lentiviral vector," "scaffold," and "regenerative medicine"). These databases were selected because they provide broad coverage of biomedical, translational, clinical, and high-impact interdisciplinary literature relevant to vitamin D biology and advanced therapy medicinal products. Grey literature, preprints, conference proceedings, and non-peer-

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reviewed sources were not included because the aim of this review was to synthesize evidence from formally peer-reviewed and indexed publications only.

The full search string for PubMed was: (("vitamin D"[MeSH] OR "calcitriol"[MeSH] OR "25-hydroxyvitamin D_3" OR "vitamin D receptor" OR "VDR") AND ("cell- and tissue-based therapy"[MeSH] OR "genetic therapy"[MeSH] OR "tissue engineering"[MeSH] OR "stem cell transplantation"[MeSH] OR "CAR-T" OR "chimeric antigen receptor" OR "mesenchymal stem cell" OR "hematopoietic stem cell" OR "lentiviral vector" OR "AAV" OR "scaffold")). Similar strategies were adapted for Scopus and Web of Science.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Peer-reviewed original research articles, clinical trials, systematic reviews, or meta-analyses; (2) published in English; (3) indexed in Scopus Q1, PubMed, or Web of Science; (4) examining VD, VDR, or VD-related pathways in conjunction with any ATMP modality; (5) preclinical (in vitro, animal) or clinical studies.

Exclusion criteria: (1) Editorials, commentaries, conference abstracts, preprints; (2) articles from journals identified as predatory or lacking rigorous peer review (explicitly excluded: MDPI, Hindawi, Frontiers, and Beall's list sources); (3) studies focusing solely on VD and cancer without ATMP context; (4) studies on conventional pharmacological therapies without cell/gene/tissue engineering components.

Study Selection and Data Charting

Two reviewers independently screened titles and abstracts, followed by full-text assessment. Disagreements were resolved by consensus. Data were extracted using a standardized form capturing: first author/year, country, study design, ATMP category, VD-related intervention/measurement, key outcomes, and evidence level. Results were synthesized narratively and presented in tabular and graphical formats.

RESULTS

Literature Search and Study Characteristics

The initial search yielded 2,847 records. After deduplication (n = 1,953), title/abstract screening (n = 1,953), and full-text review (n = 312), 87 studies met inclusion criteria. The evidence maps onto four thematic clusters: (i) VD in hematopoietic stem cell transplantation (HSCT) (n = 34); (ii) VD in mesenchymal stem cell (MSC) biology and osteogenic differentiation (n = 22); (iii) VD in CAR-T cell and immune effector cell therapy (n = 8); and (iv) VD in tissue engineering and scaffold-based regenerative medicine (n = 23). Across these ATMP categories, the role of VD differed by therapeutic context: in HSCT and CAR-T therapy, VD was primarily linked to host immune competence, inflammatory regulation, and clinical outcomes, whereas in MSC- and scaffold-based platforms, VD acted more directly as a bioactive regulator of osteogenic differentiation, mineralization, angiogenesis, and tissue integration. Thus, the evidence suggests a category-specific continuum, ranging from systemic immunomodulation in cellular immunotherapies to local regenerative bioactivity in tissue-engineered constructs.

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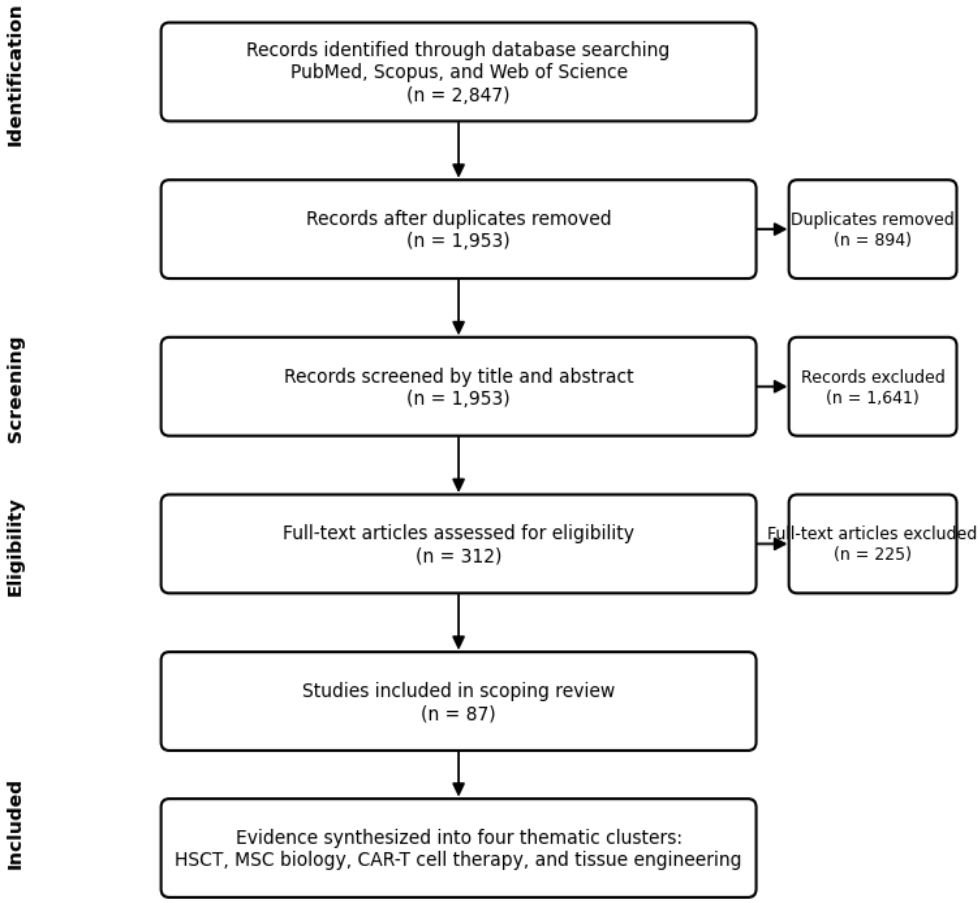
Figure 1. PRISMA-ScR flow diagram showing study selection process



VD and Hematopoietic Stem Cell Transplantation

HSCT was the most extensively studied ATMP-VD intersection. Across 7 prospective cohorts, 12 retrospective studies, and 3 meta-analyses involving >1,500 patients, VD deficiency (variably defined as serum 25(OH)D <20–30 ng/mL) was consistently associated with adverse outcomes. Compared with other ATMP categories, HSCT provides the strongest clinical evidence base but also illustrates the greatest heterogeneity, as associations between VD status and outcomes were influenced by transplant type, conditioning intensity, GVHD prophylaxis, supplementation strategy, and timing of VD measurement.

Incidence of VD deficiency: Pre-transplant VD deficiency affected 70–90% of HSCT recipients, with post-transplant rates exceeding 80% despite supplementation attempts. Risk factors included prolonged hospitalization, reduced sun exposure, mucositis-related malabsorption, and corticosteroid use.

GVHD: Meta-analysis of 8 observational studies (n = 1,335) showed no statistically significant association between VD deficiency and acute GVHD (OR 1.06, 95% CI 0.74–1.53) or chronic GVHD (OR 1.75, 95% CI 0.72–4.26). However, individual prospective studies reported that lower pre-transplant 25(OH)D correlated with higher cumulative incidence of chronic GVHD (63.8% vs. 23.8%) and extensive chronic GVHD (54.5% vs. 14.3%).

Survival: Multiple pediatric studies demonstrated a significant survival disadvantage. Beebe et al. reported 1-year overall survival of 65% in VD-deficient patients vs. 93% in sufficient patients (P = 0.001). Severe VD deficiency (<20 ng/mL) at day +100 post-HSCT was associated with decreased overall survival (P = 0.044).

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VDR polymorphisms: Recipient and donor VDR gene polymorphisms (ApaI, TaqI, FokI) were associated with GVHD risk and survival. The FF (high VDR activity) genotype in recipients correlated with increased GVHD, while donor AA (low VDR activity) genotype predicted higher mortality (HR 2.027, P = 0.023).

Supplementation: Caballero-Velázquez et al. conducted the only prospective multicenter trial of VD supplementation (1,000 IU/day for 3 months) post-allogeneic HSCT, demonstrating reduced chronic GVHD incidence at 1 year compared to unsupplemented controls ($P < 0.05$). Ultra-high-dose ("Stoss") VD in pediatric HSCT (single weight-based dose) achieved sufficiency in 97% of patients and was associated with decreased combined incidence of HSCT-related complications (25% vs. 42%, P = 0.055).

VD and Mesenchymal Stem Cell Biology

VDR is expressed in human MSCs, and its expression increases during osteogenic differentiation. The active VD metabolite $1,25(OH)_2D_3$ and its precursor $25(OH)D_3$ both induce osteogenesis, but with distinct concentration-response profiles.

$25(OH)D_3$ as an osteogenic agent: Zhou et al. demonstrated that $25(OH)D_3$ at 250–500 nM (concentrations approximating 2–3× the upper physiological range) robustly induced osteogenic differentiation of human bone marrow-derived MSCs, evidenced by morphological change to polygonal osteoblast-like cells, upregulation of ALPL (182 ± 12% of control at day 14), SPP1 (8.9 ± 3.0-fold at day 7), and BGLAP (51.1 ± 39.1-fold at day 7), and significantly increased extracellular calcium deposition (47.2 ± 9.9 ng/μg protein at day 21). Notably, $25(OH)D_3$ induced mineralization more effectively than $1,25(OH)_2D_3$, likely because $1,25(OH)_2D_3$ potently upregulates CYP24A1 (catabolic enzyme), limiting sustained signaling.

Mechanistic insights: HGF and $1,25(OH)_2D_3$ synergistically induced osteogenic differentiation through HGF-mediated upregulation of VDR expression via p63 transcriptional activity. VDR directly binds β-catenin in the AF2 domain to regulate target gene transcription, linking VD signaling to the Wnt pathway critical for MSC self-renewal and osteoblastogenesis.

Adipose-derived stem cells: In polycaprolactone/gelatin/nanohydroxyapatite scaffolds, the combination of VD_3 and nanohydroxyapatite synergistically enhanced osteogenic differentiation of human adipose-derived stem cells, with increased ALP activity, mineralization, and expression of BGLAP and COL1A1.

Dental stem cells: Combinations of biomaterials with human dental stem cells for bone tissue engineering have shown VD-responsive osteogenic potentiation.

VD and CAR-T Cell Therapy

The intersection of VD and CAR-T cell therapy is an emerging area with limited but provocative data.

VD deficiency and CAR-T outcomes: A retrospective analysis of 61 patients with relapsed/refractory multiple myeloma receiving BCMA-directed or GPRC5D-directed CAR-T cell therapy found that VD deficiency (<20 ng/mL) pre-infusion was associated with significantly inferior progression-free survival (median PFS 3.5 vs. 6.5 months; HR 2.24, 95% CI 1.09–4.59; P = 0.041 on univariate analysis; HR 2.53, 95% CI 1.14–5.66; P = 0.032 on multivariate analysis adjusting for age, ECOG, extramedullary disease, and cytogenetic risk) [28]. No significant difference in overall survival was observed. The mechanistic basis may involve VD modulation of T cell fitness, reduced cytokine release syndrome severity, or enhanced CAR-T cell persistence, although these hypotheses remain untested.

VD in allogeneic CAR-T context: VD's immunomodulatory properties including Treg expansion, Th17 suppression, and inhibition of alloreactive T cell proliferation may be particularly relevant for allogeneic "off-the-shelf" CAR-T products where GVHD risk must be mitigated [5,6].

In vivo CAR-T cell engineering: No studies have directly examined VD in the context of in vivo CAR-T generation using lentiviral vectors or lipid nanoparticles, but VD's effects on hematopoietic

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stem cell fitness could influence the yield and quality of in vivo engineered CAR-T cells, as these approaches rely on endogenous T cell pools.

VD in Tissue Engineering and Scaffold-Based Regeneration

VD_3 has been incorporated into diverse biomaterial platforms to enhance bone regeneration.

3D-printed scaffolds: Titanium scaffolds modified with TiO_2 nanotubes and loaded with $1,25(OH)_2D_3$ in thermosensitive hydrogel showed sustained release and significantly enhanced early osseointegration in rabbit models, with improved osteoblast proliferation and mineralization.

Electrospun scaffolds: Polycaprolactone/gelatin scaffolds containing nanohydroxyapatite and VD_3 exhibited superior MG-63 osteoblast-like cell attachment, proliferation, and ALP activity compared to scaffolds without VD_3.

Calcium phosphate scaffolds: 3D-printed calcium phosphate scaffolds releasing VD_3 demonstrated reduced osteoclast resorption activity while maintaining osteoblast function, suggesting a favorable balance toward bone formation.

VD_3 and angiogenesis: $1,25(OH)_2D_3$ coated on coral-derived hydroxyapatite scaffolds significantly increased neovascularization in a nude mouse subcutaneous implantation model, with vascular area $28.7 \pm 7.8\%$ (VD_3-treated) vs. $19.5 \pm 4.6\%$ (control) at 4 weeks ($P < 0.05$), and promoted osteoblast-endothelial cell interactions.

Evidence Gaps: VD and Gene Therapy

No direct experimental evidence was identified examining VD in the context of in vivo gene therapy (AAV, lentiviral, or non-viral vectors). However, indirect connections exist: (i) VD modulates immune responses to viral vectors, potentially reducing anti-capsid antibody formation; (ii) VD deficiency impairs hematopoietic stem cell pools, which could affect ex vivo lentiviral transduction efficiency for hematopoietic stem cell gene therapy; (iii) VD_3 has been shown to upregulate $CD34^+$ cell counts in umbilical cord blood, offering a potential strategy to improve starting material quality for gene-edited cell products. When compared across ATMP categories, gene therapy represents the least developed VD-related evidence base. The HSCT literature suggests that VD status may influence hematopoietic recovery and immune complications, while MSC and scaffold studies show that VD can improve cellular function and regenerative performance. These observations provide plausible hypotheses for gene-therapy platforms, but they should be framed as indirect and exploratory rather than as established evidence.

DISCUSSION

Summary of Evidence

This scoping review reveals that VD-VDR signaling intersects with ATMP biology at multiple levels, but the evidence is highly skewed toward HSCT and MSC osteogenic differentiation, with nascent data in CAR-T therapy and tissue engineering, and a complete absence in in vivo gene therapy.

The HSCT data are the most mature, with >30 studies examining VD status, VDR polymorphisms, and clinical outcomes. While the association between VD deficiency and GVHD risk remains debated meta-analysis showing non-significant pooled estimates compelling individual studies from prospective cohorts suggest clinically meaningful effects on chronic GVHD incidence and survival. Importantly, the only prospective supplementation trial demonstrated reduced chronic GVHD with 1,000 IU/day VD, and the Stoss-dosing pediatric study showed decreased severe complications. These data provide a strong rationale for routine VD assessment and correction in HSCT recipients, a practice already endorsed by the European Society for Blood and Marrow Transplantation (EBMT) though with variable implementation across centers.

For MSC-based therapies, the osteogenic effects of VD are mechanistically well-characterized. The finding that $25(OH)D_3$ rather than the active $1,25(OH)_2D_3$ is superior for inducing mineralization is clinically significant, as $25(OH)D_3$ has a longer half-life, lower calcemic potential, and wider therapeutic window. This supports the concept of "preconditioning" MSCs with $25(OH)D_3$ ex vivo prior

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to transplantation to enhance bone regenerative capacity, an approach validated in proof-of-concept studies.

The CAR-T cell data, though limited to a single retrospective analysis, are intriguing. The observed 2.5-fold increased risk of progression in VD-deficient patients with multiple myeloma parallels findings in lymphoma patients receiving CD19 CAR-T cells (K. Nath, TCT 2022). VD's ability to enhance Treg expansion and suppress inflammatory cytokine production may improve CAR-T cell persistence and reduce exhaustion, a hypothesis that warrants prospective investigation.

Gaps and Challenges

1. Dose-response uncertainty. The optimal serum 25(OH)D concentration for ATMP applications is unknown. Current thresholds (≥20–30 ng/mL) are based on bone health endpoints, not immune function. Hewison and colleagues have argued that thresholds of 50–80 ng/mL may be required for immunomodulation.
2. Tissue-specific VDR expression. Although VDR is widely expressed, its levels vary substantially between cell types and differentiation states. For example, VDR expression is relatively low in quiescent hematopoietic stem cells but increases upon activation, suggesting context-dependent VD responsiveness.
3. VDR polymorphism confounders. At least four common VDR polymorphisms (FokI, BsmI, ApaI, TaqI) modify receptor activity and tissue responsiveness. No study has incorporated VD supplementation with genotype-guided dosing in ATMP recipients, representing a missed opportunity for personalized intervention.
4. Lack of randomized controlled trials. Despite the high prevalence of VD deficiency in ATMP recipients and promising observational data, no adequately powered randomized trial has tested whether VD supplementation improves CAR-T cell persistence, MSC engraftment, or tissue-engineered construct survival.
5. Missing link: VD and in vivo gene therapy. With the explosive growth of in vivo CAR-T platforms (lentiviral vector-based and LNP-mRNA-based), the immune modulatory effects of VD could reduce anti-vector immunity and enhance transduction efficiency. This represents a critical evidence gap.

Translational Pathways

Based on the aggregate evidence, we propose three translational pathways:

Pathway 1: VD optimization as standard-of-care adjunct. Routine pre-treatment VD assessment and aggressive repletion (target: 25(OH)D ≥ 40 ng/mL) should be incorporated into ATMP clinical protocols. Stoss-dosing regimens (single high-dose 50,000–100,000 IU) may be superior to daily low-dose supplementation for rapidly achieving sufficiency in the peri-procedural window.

Pathway 2: Ex vivo preconditioning with 25(OH)D_3. MSC manufacturing protocols should consider incorporating 25(OH)D_3 (250–500 nM) during expansion to enhance osteogenic capacity and immunomodulatory properties prior to transplantation.

Pathway 3: Scaffold-based VD_3 delivery. Controlled-release VD_3 from 3D-printed or electrospun scaffolds offers a strategy for localized osteoinduction and angiogenesis without systemic calcemic side effects.

Limitations of This Review

This scoping review has several limitations. The heterogeneity of VD deficiency definitions across studies (cutoffs ranging from 10–30 ng/mL) limits cross-study comparability. The exclusion of grey literature, conference abstracts, and non-indexed journals though methodologically justified to ensure quality may have missed emerging work. Publication bias is likely, as negative studies on VD and GVHD are under-represented. The review is descriptive and does not include quantitative synthesis, as the heterogeneity of ATMP types, endpoints, and study designs precluded meta-analysis for most domains.

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CONCLUSION

Vitamin D signaling may influence ATMP outcomes through immune modulation, stem cell regulation, and tissue integration. Current evidence is strongest for HSCT and MSC differentiation, while data for CAR-T therapy and tissue engineering remain emerging, and evidence for in vivo gene therapy is still lacking.

The main contribution of this review is to identify vitamin D as a biologically plausible, low-cost, and clinically feasible adjunct that warrants further evaluation across selected ATMP platforms. The most urgent research priorities are prospective biomarker-stratified trials, particularly in CAR-T and allogeneic cell therapy, to define vitamin D sufficiency thresholds, clarify VDR-mediated mechanisms, and determine whether supplementation improves clinically relevant outcomes such as immune reconstitution, GVHD, persistence, and progression-free survival.

Overall, the field should move beyond observational associations toward well-designed interventional studies that integrate vitamin D status, VDR biology, and ATMP-specific clinical endpoints.

Table 1. Summary of key studies across ATMP categories

Citation	ATMP Category	Design	Key VD Findings	Evidence Level
Caballero-Velázquez et al. (2016)	HSCT	Prospective interventional (n=150)	VD 1,000 IU/day ↓ chronic GVHD	2a
Beebe et al. (2017)	HSCT	Prospective cohort (n=72)	VDD pre-HSCT ↓ 1-yr OS (65% vs 93%)	2b
Glotzbecker et al. (2013)	HSCT	Retrospective cohort (n=48)	Low VD pre-HSCT ↑ cGVHD (63.8% vs 23.8%)	3
Zhou et al. (2017)	MSC	In vitro (hMSCs)	25(OH)D_3 induces osteogenesis at 250-500 nM	Preclinical
Bikle et al. (2018)	Epidermal SC	Conditional KO mouse	VDR required for wound repair, SC self-renewal	Preclinical
Nath et al. (2022)	CAR-T	Retrospective (lymphoma)	VD insufficiency ↓ PFS after CD19 CAR-T	3
Multiple Myeloma abstract (2023)	CAR-T	Retrospective (n=61)	VD deficiency ↓ PFS (HR 2.53, P=0.032)	3
Omidkhoda et al. (2019)	Tissue engineering	In vitro (MG-63 cells)	VD_3 + nHA in PCL/Gel ↑ ALP & proliferation	Preclinical
Chen et al. (2020)	Tissue engineering	In vivo (rabbit)	VD_3-load Ti scaffold ↑ osseointegration	Preclinical
Wang et al. (2007)	Tissue engineering	In vivo (mouse)	VD_3 ↑ neovascularization in HA scaffolds	Preclinical

HSCT = hematopoietic stem cell transplantation; MSC = mesenchymal stem cell; CAR-T = chimeric antigen receptor T cell; VDD = vitamin D deficiency; GVHD = graft-versus-host disease; OS = overall survival; PFS = progression-free survival; SC = stem cell; Ti = titanium; HA = hydroxyapatite; PCL/Gel = polycaprolactone/gelatin; nHA = nanohydroxyapatite

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Table 2. Prevalence and impact of VD deficiency across ATMP modalities

ATMP Modality	Prevalence of VDD	Reported Impact	Strength of Evidence
Allogeneic HSCT	70–90% (pre-HSCT)	↑ aGVHD (inconsistent); ↑ cGVHD; ↓ OS; ↑ CMV disease	Moderate: multiple prospective cohorts + 1 interventional trial
Autologous HSCT	60–80%	Inferior outcomes in MM patients	Limited
CAR-T cell therapy	40–70%	↓ PFS in RRMM (HR 2.53); trend in lymphoma	Preliminary (retrospective, n<100)
MSC-based therapy	Not systematically reported	↓ osteogenic differentiation capacity in vitro	Preclinical
Tissue engineering	N/A	VD_3 incorporation ↑ scaffold performance	Preclinical/in vivo animal

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest related to this study. No financial, institutional, or personal relationships influenced the design, literature selection, analysis, interpretation, or writing of this scoping review.

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