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Polimorfisme CYP2R1 dan CYP27B1 serta Status Vitamin D terhadap Respons Imun: Tinjauan *Scoping*

CYP2R1 and CYP27B1 Polymorphisms and Vitamin D Status in Relation to Immune Responses: A Scoping Review

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Abstrak

Latar Belakang: Vitamin D berperan penting dalam regulasi sistem imun, dan polimorfisme genetik pada enzim yang terlibat dalam metabolisme vitamin D dapat memengaruhi kadar 25-hidroksivitamin D [25(OH)D] dalam sirkulasi serta luaran yang berkaitan dengan respons imun. **Tujuan:** Tinjauan *scoping* ini bertujuan untuk memetakan bukti ilmiah yang tersedia mengenai hubungan antara polimorfisme CYP2R1 dan CYP27B, status vitamin D, serta luaran terkait sistem imun dalam studi pada manusia. Metode: Tinjauan *scoping* ini dilakukan sesuai dengan pedoman PRISMA *Extension for Scoping Reviews* (PRISMA-ScR) menggunakan basis data PubMed, ScienceDirect, dan Wiley Online Library untuk artikel yang dipublikasikan pada periode 2013–2023. **Hasil:** Sebanyak delapan studi memenuhi kriteria inklusi, yang terdiri atas uji acak terkontrol, studi kohort, dan studi kasus–kontrol. Polimorfisme pada CYP2R1 secara konsisten menunjukkan hubungan yang signifikan dengan kadar 25(OH)D dalam sirkulasi serta respons terhadap suplementasi vitamin D, sedangkan varian CYP27B1 menunjukkan efek yang bervariasi bergantung pada karakteristik populasi dan konteks klinis.**Kesimpulan:** Variabilitas genetik pada CYP2R1 dan CYP27B1 memengaruhi status vitamin D dan berpotensi memodulasi luaran yang berkaitan dengan sistem imun. Namun, bukti yang secara langsung mengaitkan polimorfisme tersebut dengan fungsi imun masih terbatas, sehingga diperlukan uji klinis terstandarisasi.

Kata kunci: CYP2R1, CYP27B1, 25(OH)D3, respon imun, vitamin D

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Abstract

Background: Vitamin D plays a key role in immune regulation, and genetic polymorphisms in vitamin D–metabolising enzymes may influence circulating 25-hydroxyvitamin D [25(OH)D] levels and immune-related outcomes.

Objective: This scoping review aimed to map existing evidence on the association between CYP2R1 and CYP27B1 polymorphisms, vitamin D status, and immune-related outcomes in human studies.

Methods: A scoping review was conducted in accordance with the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines using PubMed, ScienceDirect, and Wiley Online Library for studies published between 2013 and 2023.

Results: Eight studies met the inclusion criteria, including randomised controlled trials, cohort studies, and case–control studies. Polymorphisms in CYP2R1 consistently showed significant associations with circulating 25(OH)D levels and response to vitamin D supplementation, whereas CYP27B1 variants demonstrated heterogeneous effects depending on population characteristics and clinical context.

Conclusion: Genetic variability in CYP2R1 and CYP27B1 influences vitamin D status and may modulate immune-related outcomes. However, evidence directly linking these polymorphisms to immune function remains limited, highlighting the need for standardized clinical trials.

Keywords: CYP2R1, CYP27B1, 25(OH)D3, immune response, Vitamin D

1 Introduction

Vitamin D is obtained through dietary intake or synthesized endogenously in the skin following exposure to ultraviolet B (UVB) radiation. Several factors influence cutaneous vitamin D synthesis, including latitude, season, sunscreen use, and skin pigmentation. Increased melanin content reduces UVB penetration, thereby limiting the conversion of 7-dehydrocholesterol to previtamin D_3. The resulting vitamin D molecule is biologically inactive and undergoes hepatic hydroxylation to form 25-hydroxyvitamin D [25(OH)D], which represents the primary circulating form and the most reliable biomarker of vitamin D status. Although biologically inactive, 25(OH)D serves as the substrate for further activation in target tissues. In the kidneys, 25(OH)D is converted into the active hormone 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] by the enzyme 1α-hydroxylase (CYP27B1), a process regulated by parathyroid hormone (PTH). The active hormone is subsequently inactivated by 24-hydroxylase (CYP24A1), maintaining circulating vitamin D levels through a tightly regulated negative feedback mechanism [1,2].

Beyond cutaneous synthesis, vitamin D may also be derived from dietary sources. Activation of vitamin D involves two sequential hydroxylation steps. The initial 25-hydroxylation is mediated primarily by enzymes encoded by CYP2R1 and CYP27A1, while the rate-limiting 1α-hydroxylation step is catalyzed by CYP27B1, resulting in the formation of biologically active 1,25$(OH)_2$D. Vitamin D is then either metabolically inactivated by CYP24A1 or transported to target tissues by vitamin D–binding protein (VDBP/GC) to exert its biological effects. Variations in genes encoding these enzymes may influence circulating vitamin D concentrations and individual responses to supplementation [2,3].

In addition to its classical role in calcium and bone homeostasis, vitamin D has been increasingly recognized as an important modulator of the immune system. The immune system balances protective responses against pathogens while maintaining self-tolerance, and accumulating evidence suggests that vitamin D insufficiency may increase susceptibility to infections and immune-mediated diseases, particularly in genetically predisposed individuals [3,4]

Immune cells, including macrophages, dendritic cells, T lymphocytes, and B lymphocytes, express the vitamin D receptor (VDR) and possess the enzymatic machinery required for local conversion of 25(OH)D to its active form. Upon binding to $1,25(OH)_2D$, the VDR forms a heterodimer with the retinoid X receptor (RXR) and translocates to the nucleus, where it binds to vitamin D response elements (VDREs) in the promoter regions of target genes, thereby regulating gene transcription. The expression of VDR in immune and non-skeletal tissues indicates that vitamin D exerts biological effects beyond mineral metabolism [1,5]

Importantly, extrarenal tissues, including immune cells, express CYP27B1 and are capable of locally producing active vitamin D. Unlike renal CYP27B1, extrarenal 1α-hydroxylase activity is not regulated by PTH but is instead influenced by circulating 25(OH)D concentrations and inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interferon-γ (IFN-γ). This local regulation allows vitamin D to exert paracrine and autocrine effects within immune microenvironments. Furthermore, macrophage-derived CYP24A1 is often functionally inactive due to splice variation, resulting in the absence of local negative feedback regulation [3,10,11]

Despite growing interest in the immunomodulatory role of vitamin D, substantial interindividual variability exists in circulating 25(OH)D concentrations and responses to vitamin D supplementation. Genetic polymorphisms in key vitamin D–metabolizing enzymes, particularly CYP2R1 and CYP27B1, have been proposed as important contributors to this variability. Several studies have reported associations between these polymorphisms and vitamin D status, as well as immune-related outcomes; however, the findings remain heterogeneous across populations and clinical contexts [12,14].

Therefore, this scoping review aims to systematically map and synthesise existing human studies investigating the relationship between CYP2R1 and CYP27B1 polymorphisms, circulating 25(OH)D concentrations, and immune-related outcomes. By synthesizing current evidence, this review seeks to clarify the extent to which genetic variation in vitamin D metabolism contributes to immune-related processes and to identify key gaps for future research.

2 Methods

2.1 Protocol and Eligibility Criteria

This scoping review was conducted in accordance with the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines. The review aimed to map existing evidence on the relationship between CYP2R1 and CYP27B1 genetic polymorphisms, vitamin D status, and immune-related outcomes in humans.

Eligible studies comprised all human observational and interventional study designs (e.g., randomized controlled trials, cohort studies, case–control studies, and cross-sectional studies) that examined associations between CYP2R1 and/or CYP27B1 polymorphisms and circulating vitamin D concentrations [25-hydroxyvitamin D, 25(OH)D], with outcomes related to immune response, inflammation, infection, or autoimmune conditions. Studies were included if they met the following criteria: (1) published in peer-reviewed journals; (2) conducted in human populations; (3) reporting genetic polymorphisms of CYP2R1 and/or CYP27B1; and (4) reporting vitamin D status and/or immune-related outcome.

Publications were excluded if they were duplicate records, animal or in vitro studies, narrative reviews, conference abstracts without full text, or if they provided insufficient data to extract relevant genetic, vitamin D, or immune-related information. The search period was limited to studies published between January 2013 and December 2023.

2.2 Information Sources and Search Strategy

A comprehensive literature search was conducted using three electronic databases: PubMed Central, ScienceDirect, and Wiley Online Library. The search strategy was developed to capture studies addressing vitamin D metabolism, genetic polymorphisms, and immune-related outcomes.

The following search string was applied across all databases, with minor adaptations according to database requirements: ("Vitamin D" OR "25-hydroxyvitamin D") AND (CYP2R1 OR CYP27B1) AND (immune OR inflammation OR infection OR autoimmune). Reference lists of included articles were also screened to identify additional relevant studies that may not have been captured through the electronic search.

2.3 Selection of Sources of Evidence

All records retrieved from the database search were imported into a reference management system, and duplicate records were removed. The study selection process was conducted in two stages. First, titles and abstracts were screened by one reviewer (M.A.) to assess relevance to the review objectives. Studies clearly unrelated to CYP2R1 or CYP27B1 polymorphisms, vitamin D status, or immune-related outcomes were excluded at this stage. A second reviewer (I.G.) independently evaluated records for which eligibility was unclear.

Second, full-text articles were retrieved and assessed for eligibility when abstracts did not provide sufficient information. Any disagreements between the two reviewers regarding study inclusion were resolved through discussion. When consensus could not be reached, a third reviewer (L.H.) was consulted, and final inclusion decisions were made by agreement among all three reviewers. Study selection was conducted without masking author identities, as masking has not been shown to significantly improve selection validity in scoping reviews.

2.4 Data Charting Process

Data from the included studies were charted independently by two reviewers (M.A. and I.G.) using a predefined data extraction form. Extracted information included: author and year of publication, country, study design, study population characteristics, age range, genetic polymorphisms examined, vitamin D assessment methods, intervention (if applicable), immune-related outcomes, and key findings.

Any discrepancies in data extraction were discussed and resolved through consensus, with input from a third reviewer (L.H.) when necessary. The third reviewer also verified the accuracy of the extracted data, assessed the coherence of data presentation, and ensured consistency between evidence sources and synthesized results.

2.5 Data Synthesis

Given the exploratory nature of a scoping review, results were synthesized descriptively. Studies were grouped thematically based on population characteristics and clinical context, including autoimmune conditions, infectious diseases, chronic inflammatory conditions, and general population studies. The synthesis focused on mapping patterns of evidence regarding the influence of CYP2R1 and CYP27B1 polymorphisms on vitamin D status and immune-related outcomes, as well as identifying gaps for future research (Figure 1).

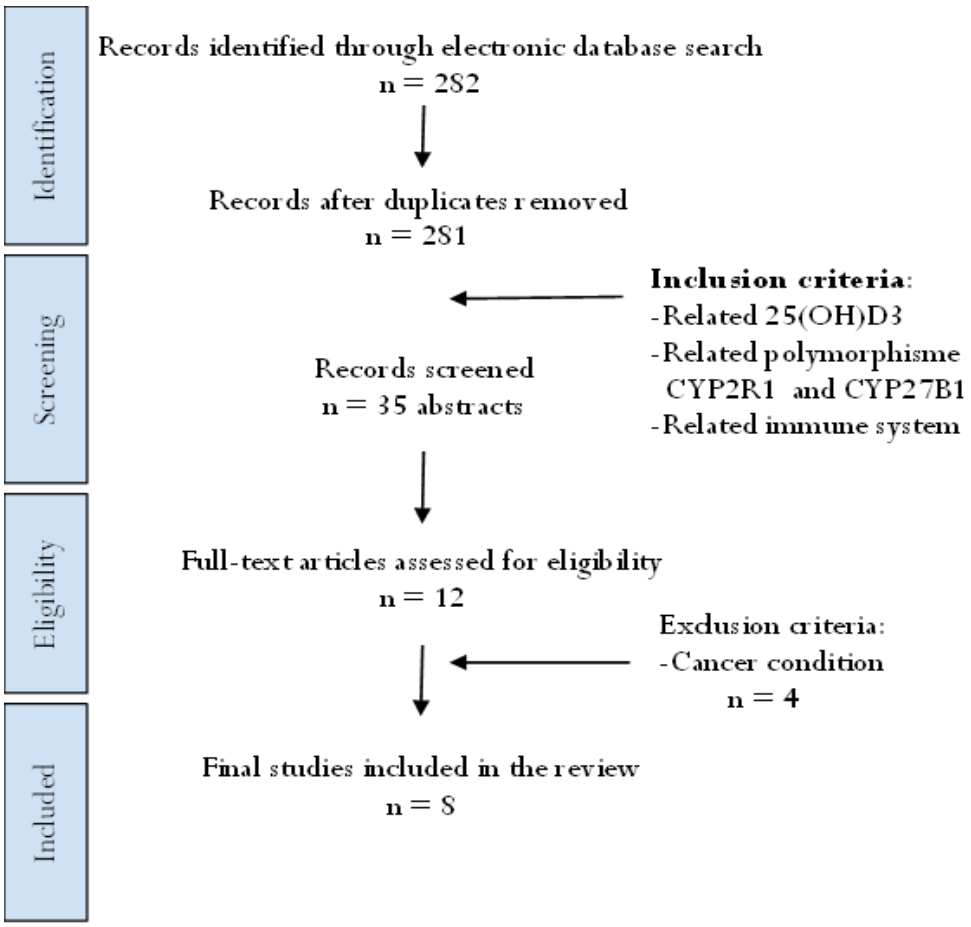

Figure 1. PRISMA-ScR study selection

2.6 Data Items and Synthesis of the Results

The publications with research on the polymorphisms CYP2R1 and CYP27B1 with concentration 25(OH)D3 and immune response made up the thematic categories of this scoping review. These two categories report and summarise results in the results section.

3 Results & Discussion

After removing duplicates and items that could not be downloaded, 281 of the 282 articles that were initially found remained. The included studies comprised six interventional studies and two observational cohort studies. Table 1 summarises the findings of each source of evidence and gives a thorough explanation of the papers.

All studies were published from 2013 until 2023. Of the eight investigations, three investigations analysed the relationship between genetic polymorphisms and CYP2R1 expression, while seven analysed the relationship between genetic polymorphisms and CYP27B1 expression. Findings varied according to study design, population characteristics, and intervention protocols. Six studies evaluated vitamin D_3 supplementation, with administered doses ranging from 14,000 IU to 140,000 IU over intervention periods of approximately 8–12 weeks. One study combined vitamin D_3 supplementation with narrow-band ultraviolet B (NB-UVB) exposure. Two observational studies with special populations such as children and older people have some results with significant polymorphism CYP2R1 and CYP27B1 with serum 25(OH)D3 concentration.

Table 1. Characteristics and result summaries of the studies included in the scoping review

Author (Year)	Country	Study Type / Design	Study Population	Age	Gene / SNPs	Intervention	Results / Summary
Ala-Houhala, Meri J.,et al (2014)	Finland	Case control trial	12 subjects with psoriasis vs 15 healthy	Psoriasis group 42.8 ± 14 y.o Healthy control group 46.1 ± 11 y.o	**CYP27B1,** CYP27A1, cathelidicin mRNA, HBD2 mRNA	Narrow-band ultraviolet B (NB-UVB) treatment Supplementation 20ug oral cholecalciferol	In the psoriasis group, NB-UVB exposure did not change CYP27A1, CYP27B1 and cathelidicin mRNA expression levels. A significant decrease was seen in the HBD2 mRNA expression level. In the control group, NB-UVB exposure significantly decreased CYP27A1, CYP27B1 and cathelidicin mRNA expression levels. A slightly increase was seen in HBD2 mRNA expression level
Waterhouse, Mary.,et al (2014)	Australia	Double blind randomized control trial	644 healthy subjects	60 to 84 y.o	**CYP2R1(rs10766197), CYP27B1 (rs10877012),** IRF4(rs12203592), MC1R(rs1805009), VDR(rs2228570), TYRP1(rs1408799), MCM6(rs182549), HERC2(rs1667394)	Placebo, Intervention 30 000 IU vitamin D3 / month, and 60 000 IU vitamin D3 / month	SNPs in CYP2R1, CYP27B1, IRF4, MC1R, VDR, TYRP1, MCM6, and HERC2 were associated with change in 25(OH)D level. CYP2R1 was significant after adjustment for multiple testing.
Schneider, Marion.,et al (2016)	Brazil	Double blind randomized control trial	38 patients on dialysis; 20 subjects were in the cholecalciferol group, 18 subjects were in the control group	-	**CYP27B1** CYP24A1 VDR IL-6 CRP PTH	Cholecalciferol (50,000 IU) twice weekly	In monocytes, while CYP27B1 and VDR expression increased in the cholecalciferol group ($p < 0.05$). CYP27B1 expression did not change, and VDR expression decreased in the control group ($p < 0.05$). There were no changes in IL-6 and CYP24A1 expression in both groups. Serum concentration of IL-6 and CRP decreased from 8.1 ± 6.6 pg/mL to 4.6 ± 4.1 pg/mL ($p < 0.05$) and from 0.50 (0.10–1.27) mg/dL to 0.28 (0.09–0.62) mg/dL ($p < 0.05$), respectively only in the cholecalciferol group. Assessed overtime, the treatment group differences in 25(OH) D, PTH, CRP and IL-6, CYP27B1 and VDR remained significant.

Carvalho, José Tarcisio G., et al (2017)	Brazil	Case Control Trial	32 dialysis patients (divided to 2 groups; 16 patients with intervention and 16 patients placebo	18 to 80 y.o	**CYP27B1**, CYP24A1 IL-6, IFN-γ, TLR7, TLR9, VDR	25 vitamin D 20ng/mL supplementation of cholecalciferol 100,000 UI/week/3 month	Reduction in the expression of TLR7, TLR9, INF-γ and CYP24A1 and an increase in VDR and CYP27B1 expression in patients which were supplemented with cholecalciferol, whereas no differences were found in the placebo group. Uremic serum increased the intracellular expression of IL-6, IFN-γ, TLR7, TLR9, VDR, CYP27B1 and CYP24A1.
Davaasambuu, et al (2017)	Mongolia	Double blind randomized control trial	390 pulmonal tuberculosis patients in intensive-phase antituberculosis treatment. Devide into intervention groups (190 subjects) and placebo group (200)	> 18 y.o	1α-hydroxylase (**CYP27B1: rs4646536**) Vitamin D receptor (rs4334089, rs11568820) 25-hydroxyvitamin D	Four biweekly doses of 3.5 mg (140,000 IU) vitamin D3	Vitamin D3 did not influence time to sputum culture conversion in the study population overall. Effects of the intervention were modified by SNPs in VDR and CYP27B1.
Mimpen, Max., et al (2021)	Netherlands	Study randomised	34 healthy subjects from the SOLARIUM study consented to genotyping.	Median age: 39.9 y.o.	**CYP27B1, (rs12368653)**, Vitamin D-Binding Protein-VDBP(rs4588 and rs7041), CYP24A1 (rs2248359),	Placebo, Vitamin D3 14,000 IU for 48 weeks	CYP27B1(rs12368653) associated with higher vitamin D level after supplementation. After 48 weeks of supplementation, carriers of the rs12368653 risk allele showed higher levels of 25(OH)D compared to non-carriers [median(IQR): 304.1 nmol/L (251.2–336.7) and 152.0 nmol/L (140.6–158.9), respectively (p = 0.014)
Çolak, Yunus., et al (2021)	Denmark	Cohort study Observation	116.335 healthy subjects randomly chosen white Danes from the Heart Study and Copenhagen General Population Study	20 to 100 y.o	**CYP2R1** (rs11791312 4, rs12794714 and rs10741657) DHCR7 (rs7944926 and rs11234027) GEMIN2 (rs2277458), HAL (rs3819817)	-	This association was strongest for genetic variants around CYP2R1. There was no observational or genetic evidence to support that 25-hydroxyvitamin D is associated with risk of urinary tract infections, skin infections, sepsis or gastroenteritis, which were used as negative control outcomes.
Das, Subhasish., et al (2022)	Bangladesh	Observational Cohort study	208 healthy children	12 to 24 months old	**CYP2R1**-rs206793 A > G,	-	SNPs for CYP27B1 (CA & CC genotype) had significant positive association (β = 1.61;

	living in urban and rural	**CYP27B1** - rs10877012 A > C GC-rs7041 T > G, rs4588 C > A, DHCR7-rs12785878 G > T)	95% CI 2.79, 0.42; p-value < 0.05) SNPs for GC-rs7041 (TT genotype GC-rs7041) had negative association (β = − 1.33; 95% CI − 0.02, − 2.64; p-value < 0.05) with vitamin-D deficiency

This scoping review synthesised evidence from eight human studies examining the role of CYP2R1 and CYP27B1 polymorphisms in relation to circulating 25(OH)D concentrations. The first two studies are about autoimmune diseases such as psoriasis and multiple sclerosis. The second category is related to infectious disease conditions which discusses the role of polymorphism in the condition of pneumonia and tuberculosis sufferers. Meanwhile, the third category discusses polymorphisms related to degenerative conditions in two studies on dialysis patients. And the last category is two population studies on children compared with the elderly.

In the Ala-Houhala et al. study, psoriasis lesions showed low vitamin D metabolising enzyme (CYP27A1, CYP27B1) and high human β-defensin-2 mRNA expression levels compared to the healthy subjects. The results showed that NB-UVB treatment significantly increased 25(OH)D in patients with psoriasis taking oral vitamin D supplementation, and the concentrations remain far from the toxicity level.In conclusion, NB-UVB treatment increases serum 25(OH)D in psoriasis patients receiving oral vitamin D supplementation significantly, yet concentrations are significantly below the toxicity range. Compared to skin treated with NB-UVB in healthy patients, healing psoriasis lesions showed a higher concentration of antimicrobial peptides but similar mRNA expression of vitamin D metabolising enzymes. NB-UVB exposure showed no effect on the levels of mRNA expression of CYP27A1, CYP27B1, or cathelicidin in the psoriasis group [7].

Another study investigated the potential effects of vitamin D-associated SNPs and risk alleles for Multiple Sclerosis (MS) on the serological response to vitamin D supplementation. In the SOLARIUM research, relapsing-remitting MS patients were randomly randomised to receive 14,000 IU of vitamin D3 or a placebo for 48 weeks. A high risk of multiple sclerosis (MS) has been associated with multiple vitamin D single nucleotide polymorphisms (SNPs), including low 25(OH)D) status. However, studies investigating the benefits of vitamin D administration in MS patients have shown inconsistent results [12].

Research by Colak et al. indicates that vitamin D might regulate the innate immune system. Low plasma 25-hydroxyvitamin D concentrations have been associated with an increased risk of respiratory tract infections in adults, children, and newborns, according to observational studies. This randomised controlled study indicates that vitamin D supplementation may help prevent acute respiratory tract infections. The most significant correlation between this phenomena and genetic polymorphisms around CYP2R1 was observed. Observational or genetic data did not support the risk of gastroenteritis, skin infections, sepsis, or urinary tract infections, which were used as unfavourable control outcomes. In conclusion, low vitamin D levels are associated with an increased risk of bacterial pneumonia, both observationally and genetically [6].

In addition, the study by Davaasambuu et al. demonstrated that high-dose vitamin D_3 supplementation (3.5 mg [140,000 IU] administered four times over eight weeks) significantly increased serum 25-hydroxyvitamin D concentrations in patients with pulmonary tuberculosis. Although vitamin D_3 supplementation did not reduce the time to sputum culture conversion in the overall study population, the effect of the intervention was modified by genetic polymorphisms in the vitamin D receptor (VDR) and CYP27B1, indicating genotype-specific differences in treatment response [8]. According to a study by Carvalho et al., vitamin D regulates the immune system in dialysis

patients. It's uncertain if vitamin D replacement affects dialysis patients' lymphocytes' inflammatory responses [5]. These findings suggest that cholecalciferol supplementation may enhance the expression of vitamin D regulatory enzymes in lymphocytes under uremic conditions [11]. Relevant to the investigation of Meireles et al. patients on dialysis frequently have hypovitaminosis D and inflammation, and it is widely known that these conditions have been associated to a lower chance of survival. After receiving 50,000 IU of cholecalciferol twice a week for 12 weeks, the cholecalciferol group's serum 25(OH)D developed from 14.3 ± 4.7 ng/mL to 43.1 ± 11.0 ng/mL ($p < 0.05$), but the control group did not change (13.9 ± 4.2 ng/mL to 13.5 ± 4.3 ng/mL; p ¼ 0.56). In monocytes, the cholecalciferol group indicated an increase in both CYP27B1 and VDR expression ($p<0.05$), although the control group showed a decrease in both CYP27B1 and VDR expression ($p<0.05$). Consequently, the findings indicate that the restoration of vitamin D status in dialysis patients resulted in an increase in CYP27B1 and VDR expression in monocytes as well as a decrease in circulating inflammatory markers [11].

Das S. et al. conducted an observational study to investigate the prevalence and risk factors of vitamin D deficiency in children aged 12 to 24 months living in urban and rural Bangladesh. Serum 25-hydroxyvitamin D (free 25(OH)D) levels, food consumption, sun exposure, anthropometric status, sociodemographic status, and single nucleotide polymorphisms in vitamin-D pathway genes were evaluated in 208 children. A vitamin D insufficiency was present in 47% of the children (free 25(OH)D 50 nmol/l) [7]. According to this research, vitamin D deficiency was linked to common variations in the vitamin D pathway genes (CYP27B1 and GC) in both Bangladesh children living in rural and urban areas. Additionally, they discovered that the length of time spent in the sun and breastfeeding had a negative correlation with the result. This study investigated the function of single nucleotide polymorphisms (SNPs) in pathway genes (GC-rs7041 T > G, rs4588 C > A, CYP2R1-rs206793 A > G, CYP27B1-rs10877012 A > C, and DHCR7-rs12785878 G > T). Significant differences in serum vitamin D levels between genotypes were found [7].

According to this study, children's vitamin D levels were higher in those with wild type genotypes of CYP2R1-rs2060793 (AA), CYP27B1-rs10877012 (AA), and GC-rs4588 (CC). On the other hand, children with GC-rs7041 (TT) and DHCR7-rs12785878 (GG) wild type genotypes had decreased vitamin D levels. The vitamin D-25-hydroxylase enzyme is encoded by the CYP2R1 gene, which has been linked to circulating levels of 25(OH) D. In our investigation, children with the AA genotype of CYP2R1 had higher levels of 25(OH)D, while those with the GG genotype showed lower levels. There is a significant correlation between this gene and vitamin D status. According to this studies, children with the CYP27B1 genotype AA had higher levels of 25(OH) D than children with the genotypes CC and CA.

Based to studies by Waterhouse et al., conditions in older populations explained 24% of the difference in responsiveness to supplementation. Body mass index, background UV radiation, and self-reported health status all contributed marginally more. Changes in 25(OH)D levels were associated with SNPs for CYP2R1, IRF4, MC1R, CYP27B1, VDR, TYRP1, MCM6, and HERC2. However, after accounting for repeated testing, only CYP2R1 remained significant. Comparable amounts of heterogeneity in response to supplementation were explained by models combining SNPs and models including personal and environmental factors.[14] Stepwise regression analyses imply that genetic variability might be related to supplement response, meaning that there might be variation in the physiologically normal level of 25(OH)D or that some individuals would require higher doses to achieve optimal levels.

Summary of Evidence

This scoping review synthesised evidence from eight human studies published between 2013 and 2023 examining the relationships between CYP2R1 and CYP27B1 genetic polymorphisms, circulating 25-hydroxyvitamin D [25(OH)D] concentrations, and immune-related outcomes. The

included studies comprised interventional and observational designs conducted across diverse populations, including children, older adults, patients with autoimmune or infectious diseases, and individuals with chronic kidney disease.

Across the reviewed literature, vitamin D status emerged as a central intermediate phenotype linking genetic variation to immune-related outcomes. Several studies demonstrated that vitamin D supplementation modulated inflammatory markers, antimicrobial peptide expression, and immune regulatory enzymes, supporting the role of vitamin D as an immunomodulatory agent [1,3,5,11]. However, immune-related effects were predominantly assessed indirectly, and few studies measured direct immune cell functional outcomes.

Polymorphisms in CYP2R1 were consistently associated with baseline serum 25(OH)D concentrations and responsiveness to vitamin D supplementation across multiple populations. Interventional and population-based studies reported that genetic variants near CYP2R1 explained a significant proportion of interindividual variability in circulating vitamin D levels, even after adjustment for environmental and personal factors [6,14]. This consistency underscores the importance of CYP2R1 as a key determinant of systemic vitamin D availability.

In contrast, evidence regarding CYP27B1 polymorphisms was more heterogeneous. Several studies identified associations between CYP27B1 variants and serum 25(OH)D concentrations, inflammatory markers, or supplementation response; however, these associations varied by clinical context and population [5,7,8,12]. Given the role of CYP27B1 in both renal and extrarenal activation of vitamin D, particularly within immune cells, these findings suggest that CYP27B1 polymorphisms may influence immune-related processes in a context-dependent manner rather than exerting uniform systemic effects.

Overall, the evidence indicates that genetic variation in vitamin D–metabolizing enzymes contributes to differences in vitamin D status and supplementation response, while direct links between these polymorphisms and immune function remain limited and insufficiently characterised.

Limitations

This scoping review has several limitations that should be considered when interpreting the findings. First, consistent with the nature of a scoping review, the primary objective was to map and summarise existing evidence rather than to formally assess study quality or establish causal relationships. Consequently, no risk-of-bias assessment was performed, which limits the ability to draw definitive conclusions regarding causality between genetic polymorphisms, vitamin D status, and immune-related outcomes [13].

Second, although a comprehensive search across multiple databases was conducted, the number of eligible studies was limited, and the available evidence demonstrated substantial heterogeneity in study design, population characteristics, vitamin D supplementation regimens, and immune-related outcome measures. Such heterogeneity precluded quantitative synthesis and restricted direct comparison across studies [6,14].

Third, variations in population demographics, including age, ethnicity, geographic location, and underlying clinical conditions, may have contributed to inconsistencies in reported associations between CYP2R1 and CYP27B1 polymorphisms and circulating 25(OH)D concentrations. Previous studies have shown that genetic effects on vitamin D metabolism may differ across populations, further limiting the generalisability of the findings [1,6].

Finally, definitions of vitamin D deficiency and insufficiency varied across the included studies, with differing cut-off values and classification schemes for serum 25(OH)D concentrations. Such inconsistencies have been widely reported in vitamin D research and may influence the interpretation and comparability of study results [3,9].

Despite these limitations, this scoping review provides a structured overview of the current state of evidence and identifies important gaps for future research integrating genetic, biochemical, and immunological approaches.

4 Conclusions

Based on the available evidence, this scoping review identifies CYP2R1 polymorphisms as the most consistent genetic determinants of circulating 25-hydroxyvitamin D levels across diverse human populations. Variants in CYP2R1 were repeatedly associated with baseline vitamin D status and magnitude of response to vitamin D supplementation, supporting the biological role of CYP2R1 as a key hepatic 25-hydroxylase [6,14].

In contrast, associations involving CYP27B1 polymorphisms were more variable and appeared to depend on population characteristics, disease states, and local immune regulatory mechanisms. While CYP27B1 plays a critical role in the activation of vitamin D within immune cells, current evidence suggests that its genetic variants exert context-specific effects, primarily mediated through modulation of vitamin D availability rather than direct immune gene regulation [5,8,11].

Importantly, most studies reviewed assessed immune-related outcomes indirectly, and heterogeneity in study design, vitamin D dosing, immune endpoints, and definitions of vitamin D deficiency limits causal inference. Consequently, while genetic variation in CYP2R1 and CYP27B1 contributes to interindividual differences in vitamin D status, evidence directly linking these polymorphisms to immune function remains insufficient.

Future research should prioritise well-designed clinical studies integrating genetic profiling, standardised vitamin D interventions, and clearly defined immune endpoints to clarify the clinical relevance of vitamin D–related genetic variability. Such approaches may support the development of more personalised vitamin D supplementation strategies in populations at risk of immune-related disorders.

5 Declaration

5.1 Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

5.2 Author Contributions

All authors contributed to the conception and design of the study. Material preparation, data collection, and analysis were performed by the authors. All authors read and approved the final manuscript.

5.3 Ethical Approval

This study was conducted as a scoping review based exclusively on previously published literature. No human participants or animals were directly involved in this study; therefore, ethical approval was not required.

5.4 Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

6 References

[1] Das, S., Hasan, M. M., Mohsin, M., Jeorge, D. H., Rasul, M. G., Khan, A. R., Gazi, M. A., & Ahmed, T. (2022). Sunlight, dietary habits, genetic polymorphisms and vitamin D deficiency in urban and rural infants of Bangladesh. *Scientific Reports*, *12*(1). https://doi.org/10.1038/s41598-022-07661-y

[2] Aranow, C. (2011). Vitamin D and the Immune System. *Journal of Investigative Medicine : The Official Publication of the American Federation for Clinical Research*, *59*(6), 881. https://doi.org/10.231/JIM.0B013E31821B8755

[3] Asghari, A., Jafari, F., Jameshorani, M., Chiti, H., Naseri, M., Ghafourirankouhi, A., Kooshkaki, O., Abdshah, A., & Parsamanesh, N. (2022). Vitamin D role in hepatitis B: focus on immune system and genetics mechanism. *Heliyon*, *8*(11). https://doi.org/10.1016/j.heliyon.2022.e11569

[4] Ashique, S., Gupta, K., Gupta, G., Mishra, N., Singh, S. K., Wadhwa, S., Gulati, M., Dureja, H., Zacconi, F., Oliver, B. G., Paudel, K. R., Hansbro, P. M., Chellappan, D. K., & Dua, K. (2023). Vitamin D—A prominent immunomodulator to prevent COVID-19 infection. *International Journal of Rheumatic Diseases*, *26*(1), 13–30. https://doi.org/10.1111/1756-185X.14477

[5] Carvalho, J. T. G., Schneider, M., Cuppari, L., Grabulosa, C. C., Aoike, D. T., Redublo, B. M. Q., Batista, M. C., Cendoroglo, M., Moyses, R. M., & Dalboni, M. A. (2017). Cholecalciferol decreases inflammation and improves Vitamin D regulatory enzymes in lymphocytes in the uremic environment: A randomized controlled pilot trial. *PLoS ONE*, *12*(6). https://doi.org/10.1371/journal.pone.0179540

[6] Çolak, Y., Nordestgaard, B. G., & Afzal, S. (2021). Low vitamin D and risk of bacterial pneumonias: Mendelian randomisation studies in two population-based cohorts. *Thorax*, *76*(5), 468–478. https://doi.org/10.1136/thoraxjnl-2020-215288

[7] Ala-Houhala, M. J., Karppinen, T., Vähävihu, K., Kautiainen, H., Dombrowski, Y., Snellman, E., Schauber, J., & Reunala, T. (2014). Narrow-band ultraviolet B treatment boosts serum 25-hydroxyvitamin D in patients with psoriasis on oral vitamin D supplementation. *Acta Dermato-Venereologica*, *94*(2), 146–151. https://doi.org/10.2340/00015555-1685

[8] Ganmaa, D., Munkhzul, B., Fawzi, W., Spiegelman, D., Willett, W. C., Bayasgalan, P., Baasansuren, E., Buyankhishig, B., Erdene, S. O., Jolliffe, D. A., Xenakis, T., Bromage, S., Bloom, B. R., & Martineau, A. R. (2017). High-dose Vitamin D3 during tuberculosis treatment in Mongolia a randomized controlled trial. *American Journal of Respiratory and Critical Care Medicine*, *196*(5), 628–637. https://doi.org/10.1164/rccm.201705-0936OC

[9] L Bishop, E., Ismailova, A., Dimeloe, S., Hewison, M., & White, J. H. (2021). Vitamin D and Immune Regulation: Antibacterial, Antiviral, Anti-Inflammatory. *JBMR Plus*, *5*(1). https://doi.org/10.1002/JBM4.10405

[10] Mailhot, G., & White, J. H. (2020). Vitamin D and Immunity in Infants and Children. *Nutrients 2020, Vol. 12, Page 1233*, *12*(5), 1233. https://doi.org/10.3390/NU12051233

[11] Meireles, M. S., Kamimura, M. A., Dalboni, M. A., Giffoni de Carvalho, J. T., Aoike, D. T., & Cuppari, L. (2016). Effect of cholecalciferol on vitamin D-regulatory proteins in monocytes and on inflammatory markers in dialysis patients: A randomized controlled trial. *Clinical Nutrition*, *35*(6), 1251–1258. https://doi.org/10.1016/j.clnu.2016.04.014

[12] Mimpen, M., Rolf, L., Poelmans, G., den Ouweland, J. van, Hupperts, R., Damoiseaux, J., & Smolders, J. (2021). Vitamin D related genetic polymorphisms affect serological response to high-dose vitamin D supplementation in multiple sclerosis. *PLoS ONE*, *16*(12 December). https://doi.org/10.1371/journal.pone.0261097

[13] van Etten, E., Stoffels, K., Gysemans, C., Mathieu, C., & Overbergh, L. (2008). Regulation of vitamin D homeostasis: implications for the immune system. *Nutrition reviews*, *66*(10 Suppl 2), S125–S134. https://doi.org/10.1111/j.1753-4887.2008.00096.x

[14] Waterhouse, M., Tran, B., Armstrong, B. K., Baxter, C., Ebeling, P. R., English, D. R., Gebski, V., Hill, C., Kimlin, M. G., Lucas, R. M., Venn, A., Webb, P. M., Whiteman, D. C., & Neale, R. E. (2014). Environmental, personal, and genetic determinants of response to vitamin D supplementation in older adults. *Journal of Clinical Endocrinology and Metabolism*, *99*(7). https://doi.org/10.1210/jc.2013-4101

[15] Yamamoto, E., & Jørgensen, T. N. (2019). Immunological effects of vitamin D and their relations to autoimmunity. *Journal of Autoimmunity*, *100*, 7–16. https://doi.org/10.1016/j.jaut.2019.03.002