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Vitamin D as an immunomodulator in selected infectious diseases

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ABSTRACT

Vitamin D deficiency has become a widespread global health concern, particularly in industrialized societies, where limited sun exposure reduces endogenous synthesis. The aim of this review is to summarize current knowledge regarding the role of vitamin D in immune regulation, with particular emphasis on some of the infectious diseases. This review focuses on recent experimental and clinical studies exploring the mechanisms of vitamin D action and their clinical relevance. The active form of vitamin D enhances antimicrobial peptide production (defensins), modulates cytokine responses, and affects the differentiation and function of immune cells, including dendritic cells and T lymphocytes, through Toll-like receptors. By facilitating intracellular communication vitamin D may also help to maintain epithelial barrier integrity. Observational clinical studies suggest an association between low vitamin D levels and increased susceptibility to infections. The observational nature of these studies, however, does not provide certainty as to the validity of the theses put forward based on the observed correlations.

Keywords: vitamin D, general medicine, immunomodulation, infection

1. INTRODUCTION

With fewer people working in agriculture and more living in the cities, conducting more of a modern type of lifestyle, it is clear that more and more people in developing countries are likely to spend less time outdoors. Cutaneous synthesis of vitamin D through sun exposure is often far too insufficient to meet physiological needs. It may result in poor immune function. Dietary intake, obesity, aging, and some chronic diseases also lead to worsening of the immune state. The respiratory system remains in constant contact with numerous pathogens, some of which are capable of significantly reducing the quality of life or even contributing to premature mortality. The body's ability to combat these pathogens is crucial for the prevention of infectious diseases and depends on many biological factors, including the availability of vitamin D. Until the second half of the 20th century, researchers knew only the bone-mineralization function of vitamin D and its relationship to rickets. In the 1980s, a breakthrough happened - the presence of vitamin D receptor (VDR) was demonstrated in numerous tissues, including immune cells such as T and B lymphocytes, monocytes, and macrophages. This finding suggested that the

active form of vitamin D, 1,25$(OH)_2D_3$ (calcitriol), can function as an endocrine, paracrine, and autocrine regulator of the immune response (Provvedini et al., 1983).

Twenty years later, clinical and molecular studies provided even more convincing evidence that vitamin D influences both innate and adaptive immunity (Aranow, 2011; Haussler et al., 2013). Among numerous mechanisms, the ability to stimulate the expression of antimicrobial peptides (such as cathelicidin) was demonstrated. Vitamin D was also shown to modulate the production of pro- and anti-inflammatory cytokines and participate in the regulation of T-cell differentiation (Liu et al., 2006).

2. REVIEW METHODS

A narrative literature review was carried out to summarize existing evidence on the immunomodulatory role of vitamin D in certain infectious diseases. A literature search was performed using PubMed and Google Scholar. In addition, the reference lists of relevant articles were manually screened to identify further studies relevant to the topic. The search strategy used combinations of the following keywords: “vitamin D”, “immunomodulation”, “innate immunity”, “adaptive immunity”, “cathelicidin”, “CAMP”, “respiratory tract infections”, “community-acquired pneumonia”, and “urinary tract infection”. Original research papers, randomized controlled trials, observational studies, meta-analyses, and relevant review articles written in English were included.

The study selection process is summarized in Figure 1. The selection of articles was based on their relevance to vitamin D metabolism, immune regulation mechanisms, and links with infectious diseases. Duplicate records, non-English publications, and studies not fitting within the scope of this review were excluded.

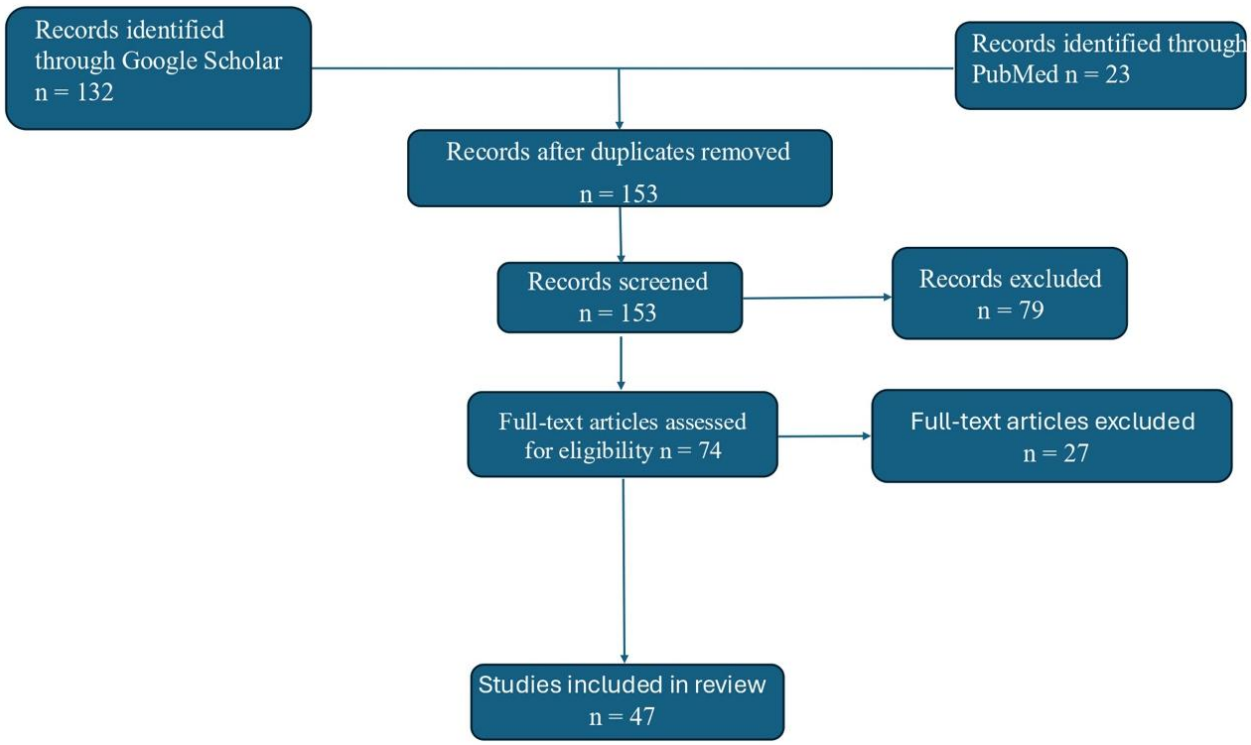

Figure 1. PRISMA chart illustrating the literature search and study selection process.

3. RESULTS AND DISCUSSION

Vitamin D: Metabolism

The synthesis of vitamin D (D_3) in the skin doesn’t require any enzyme. Cholecalciferol is produced from 7-dehydrocholesterol (7-DHC) through a two-step mechanism. Under ultraviolet UVB (280–320 nm) coming from the Sun, the B ring gets broken, resulting in the formation of pre-D_3, which then undergoes a temperature-dependent isomerization to D_3 (Bikle, 2014). The rate of vitamin D_3 production depends both on the intensity of UVB radiation and the degree of skin pigmentation (Holick et al., 1980). Melanin reduces the penetration of UVB radiation to 7-DHC, thereby limiting D_3 synthesis; a similar effect is observed with clothing and sunscreen use.

The amount of UVB radiation reaching the Earth's surface varies with season and latitude, meaning that the further one lives from the equator, the shorter the period during which cutaneous synthesis can meet the body's vitamin D requirements.

Vitamin D may also be obtained from the diet. Unfortunately, its amounts are generally low in most foods. Among reasonable D_3 sources are fatty fish (Lu et al., 2007). Compared to D_3, vitamin D_2 differs structurally by the presence of an additional double bond between carbon atoms C22 and C23 and a methyl group at C24 in the side chain. These structural differences affect the pharmacokinetic properties of vitamin D_2, including its lower affinity for vitamin D–binding protein (DBP), resulting in faster clearance from circulation. D_2 is also less likely to get converted to 25-hydroxyvitamin D (25OHD) by certain 25-hydroxylases and alter its catabolism via 24-hydroxylase (CYP24A1) (Houghton and Vieth, 2006). Consequently, unless administered daily, supplementation with vitamin D_2 results in lower serum 25OHD levels than equivalent doses of vitamin D_3 (Tripkovic et al., 2012). However, it should be emphasized that the active metabolites $1,25(OH)_2D_2$ and $1,25(OH)_2D_3$ exhibit similar affinity for the vitamin D receptor (VDR).

Almost all vitamin D metabolites in the bloodstream are bound to vitamin D–binding protein (DBP); however, this bound fraction is generally not available to most cells. According to the so-called free hormone hypothesis, it is the free (unbound) fraction that is biologically active, as it can enter cells and exert physiological effects, whereas DBP primarily serves as a circulating reservoir for vitamin D metabolites (Bikle, 2014). Evidence supporting this concept comes from studies in DBP knockout mice and observations in humans with mutations in the DBP gene.

In mice lacking DBP, despite very low serum levels of total 25(OH)D and $1,25(OH)_2D$, no signs of vitamin D deficiency were observed, and tissue levels of active vitamin D, as well as markers of its biological activity, remained normal (Bikle, 2014). Similar findings have been reported in a human subject with a deletion of the DBP gene: despite very low total vitamin D metabolite levels, serum calcium, phosphate, and parathyroid hormone remained within normal ranges during vitamin D supplementation, and free 25(OH)D levels were near normal. These findings support the free hormone hypothesis and suggest that free 25(OH)D concentration may be a better indicator of vitamin D status than total 25(OH)D, especially given that DBP levels can vary in different clinical conditions, such as liver disease, nephrotic syndrome, pregnancy, trauma, and inflammatory states (Bikle et al., 2017; Malmstroem et al., 2017).

Vitamin D: Mechanism of Action

CAMP

Rapid recognition and elimination are needed to prevent the development of infection. One of the key elements of this response is the activation of Toll-like receptors (TLRs), which belong to the group of pathogen recognition receptors, in monocytes. Their activation induces antimicrobial peptides, including cathelicidins, which participate in bacterial killing. Cathelicidins are a family of proteins derived from a precursor molecule. The broad antimicrobial activity is attributed to a 37-amino-acid peptide located in the C-terminal region, which is generated by proteolytic cleavage of the pro-peptide fragment (Gombart et al., 2005). The only known human cathelicidin, hCAP18 (the C-terminal domain of human cationic antimicrobial protein 18, also referred to as LL-37), is encoded by the human cathelicidin antimicrobial peptide (CAMP) gene. Although initially identified in neutrophils, CAMP expression has also been demonstrated in dendritic cells, lymphocytes, monocytes, natural killer (NK) cells, and epithelial cells of the skin, respiratory tract, and even gastrointestinal tract (Gombart et al., 2005). The CAMP gene product exhibits broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria.

The active form of vitamin D—$1,25(OH)_2D_3$—is recognized as an important regulator of CAMP expression not only in monocytes, but also in epithelial cells of the lungs and intestines, keratinocytes, and placental trophoblasts (Gombart et al., 2005; Liu et al., 2009a; Schauber et al., 2008; Yim et al., 2007). $1,25(OH)_2D_3$ upregulates TLR2/1 and CAMP expression, resulting in enhanced antimicrobial activity against Staphylococcus aureus (Schauber et al., 2008). The role of $1,25(OH)_2D_3$ as an autocrine or paracrine regulator during pregnancy is reflected in its ability to induce CAMP expression in placental trophoblasts, a process that occurs independently of TLR signaling (Liu et al., 2009a). Similarly, the induction of CAMP in lung epithelial cells by $1,25(OH)_2D_3$, accompanied by increased antibacterial activity, is also independent of TLR signaling (Yim et al., 2007). The antimicrobial mechanism of CAMP involves, among others, the attraction of the positively charged peptide to the bacterial membrane through interactions with negatively charged surface components. The accumulation of CAMP induces stress within the lipid bilayer, followed by translocation of the peptide from the outer to the inner membrane, ultimately disrupting bacterial membrane homeostasis.

Recent studies have shown that the transcription factor C/EBPα is a potent activator of CAMP gene transcription in lung epithelial cells. Moreover, it functionally cooperates with the vitamin D receptor (VDR) and the Brm protein, a component of the SWI/SNF

chromatin remodeling complex, to regulate CAMP expression (Dhawan et al., 2015). Given the growing problem of antibiotic resistance, these findings suggest that modulation of innate immunity may represent an alternative approach that does not rely on antibiotic therapy. Further research has demonstrated that histone acetylation may enhance the regulatory effect of $1,25(OH)_2D_3$ on CAMP expression across different cell types (Schauber et al., 2008; Termén et al., 2008). Therefore, histone deacetylase inhibitors are being considered a novel approach to strengthen innate immunity in the treatment of bacterial infections. In addition to cathelicidin, $1,25(OH)_2D_3$ acting via the VDR may also interact with TLR-induced interleukin-1β (IL-1β) signaling, leading to increased expression of another antimicrobial peptide—β-defensin 4 (DEFB4, formerly known as HBD2)- in monocytes (Liu et al., 2009).

Dendritic Cells

Calcitriol regulates the immune response by influencing the function of dendritic cells (DCs) and lymphocytes. DCs have been shown to convert 25-hydroxyvitamin D_3 into calcitriol, leading to autocrine and paracrine effects within the immune microenvironment. It leads to the development of a so-called tolerogenic phenotype of dendritic cells, which limits excessive T-cell activation and supports the expansion of regulatory cells. Moreover, vitamin D_3 can also affect the migration of dendritic cells and the trafficking patterns of T lymphocytes as demonstrated by Bscheider and Butcher, (2016). Locally increased concentrations of vitamin D in the skin, resulting from UVB exposure, may direct T cells toward cutaneous tissues by regulating chemokine receptor expression, while simultaneously suppressing their migration to the gut (Sigmundsdottir et al., 2007). This mechanism suggests that vitamin D may contribute to the shaping of tissue-specific immune responses. This may lead to changes in the nature of the immune response, namely the promotion of regulatory pathways and the attenuation of inflammatory reactions. This mechanism suggests that vitamin D may contribute to the shaping of tissue-specific immune responses. Furthermore, the presence of calcitriol during dendritic cell activation alters their ability to migrate to lymph nodes and influences antigen presentation to T cells (Sigmundsdottir et al., 2007). It may all lead to changes in the nature of the immune response, namely, the promotion of regulatory pathways and the attenuation of inflammatory reactions, as illustrated in Table 1. It summarizes the principal mechanisms involved in vitamin D-mediated immune regulation.

Table 1. Immunological mechanisms of vitamin D.

Mechanism	*Key molecule*	*Cell type*	*Effect*
Induction of antimicrobial peptides	LL-37 (cathelicidin)	Macrophages, epithelial cells	Direct antimicrobial activity
Upregulation of defensins	β-defensins	Epithelial cells	Enhanced pathogen killing
Modulation of TLR signaling	TLR2/1	Monocytes	↓ inflammatory response
Cytokine regulation	Il-6, TNF-α	Immune cells	↓ pro-inflammatory cytokines
Enhancement of autophagy	–	Macrophages	Improved pathogen clearance
Strengthening epithelial barrier	Claudins, occludin, ZO-1	Epithelial cells	↑ barrier integrity

Gap Junctions

Vitamin D_3 (cholecalciferol) also promotes intercellular communication through gap junctions in murine fibroblasts (C3H/10T1/2 cells) at concentrations ranging from 0.01 to 1.0 μM, as demonstrated by dye transfer using Lucifer yellow CH (Stahl et al., 1994). Molecular imaging is included in figure 2. Vitamin D_2 exerts a similar stimulatory effect on cell–cell communication. At higher concentrations of vitamin D_3 (5 μM), gap junction communication is strongly inhibited. This suppression can be reversed, and communication can be restored by treatment with all-trans retinoic acid (1 μM) after vitamin D_3 is removed from the culture medium. In contrast, cells initially stimulated with retinoic acid (1 μM) show a rapid decline in intercellular communication when the retinoid is replaced with vitamin D_3 (5 μM). These findings suggest that vitamin D plays a regulatory role in intercellular communication. This previously unrecognized function may partly explain the antiproliferative effects of vitamin D observed in certain cancers (Stahl et al., 1994).

Tight junctions

An experimental study conducted by Zhang et al., (2022) reveals another interesting role that vitamin D plays - namely, how it regulates tight junction proteins, which are responsible for maintaining healthy intestinal barrier integrity. VDRE - vitamin D response elements are included in this process, which are associated with the CLDN-5 gene. Its enhanced transcription directly improves barrier function. In contrast, VDR deficiency is more commonly associated with reduced Claudin-5 expression, increased intestinal

permeability, and enhanced inflammatory responses. Increased VDR activity or vitamin D_3 supplementation results in upregulation of tight junction proteins and improved epithelial barrier integrity.

Other Mechanisms

Studies also indicate that vitamin D may interact with other immune-regulating pathways, including vitamin A metabolism and its active metabolite, retinoic acid (Mora et al., 2008). The interplay between these systems may influence both the differentiation and migration of immune cells. Vitamin D may also enhance antimicrobial responses within innate immunity include the induction of reactive oxygen species and the activation of antibacterial autophagy (Shin et al., 2010).

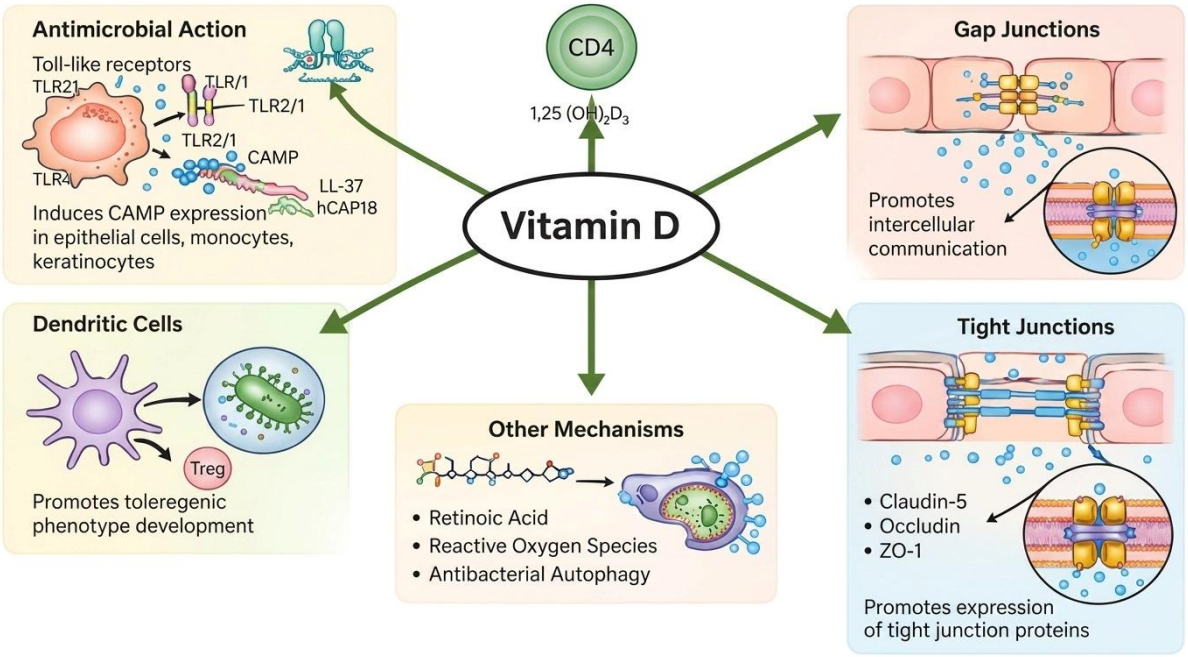

Figure 2. Immunological mechanisms of vitamin D.

Vitamin D and Infectious Diseases

Vitamin D and the common cold

The common cold is an infectious disease caused by more than 200 different viruses. Most commonly, rhinoviruses, coronaviruses, enteroviruses, adenoviruses, and parainfluenza viruses. Improved protection against these numerous pathogens may reduce the incidence of infections or lead to a milder disease course. In elderly patients, as well as in individuals with diabetes or receiving immunosuppressive therapy, reduced susceptibility to infections may also contribute to lower mortality. The study by Rondanelli et al., (2018) clarifies this issue by presenting correlational data highlighting the significant role of vitamin D in supporting immune function.

A study that provides important evidence for the immunostimulatory effect of vitamin D is the meta-analysis by Martineau et al., (2017) which included 25 randomized clinical trials and demonstrated that vitamin D supplementation is safe and may reduce the risk of acute respiratory tract infections. The greatest benefits were observed in individuals with significant vitamin D deficiency and in those receiving regular dosing rather than large bolus doses. Epidemiological studies further suggest that higher vitamin D levels are associated with a lower risk of upper respiratory tract infections, such as the common cold. In some analyses, supplementation with 4000 IU/day significantly increased the likelihood of remaining infection-free during the observation period, supporting the rationale for monitoring vitamin D status in adults with recurrent respiratory infections and correcting deficiencies (Bergman et al., 2015).

The role of vitamin D appears particularly important in pediatric populations. In studies conducted among Mongolian children, consumption of milk fortified with 300 IU of vitamin D_3 significantly reduced the risk of acute respiratory infections during winter in children with vitamin D deficiency (Camargo et al., 2012). Higher vitamin D levels in infants have also been associated with greater resistance to respiratory infections (Khakshour et al., 2015). Supplementation in this age group may support infection prevention, and

when combined with vaccination, may reduce the incidence of upper respiratory tract infections and antibiotic use, potentially limiting the development of bacterial resistance.

Additionally, supplementation with 1200 IU/day during the winter season may reduce the incidence of influenza A by enhancing innate immunity and increasing the production of antimicrobial peptides (Urashima et al., 2010). In young adults, a preventive effect of weekly supplementation with 10,000 IU of vitamin D_3 on upper respiratory tract infections has also been demonstrated (Camargo et al., 2012). However, not all studies confirm a protective effect of vitamin D. Some analyses did not show a significant association between vitamin D levels and the incidence or severity of lower-tract infections. Even with daily supplementation of 2000 IU. Similarly, high doses administered as single or monthly boluses have not consistently reduced the incidence of the common cold or upper respiratory tract infections (Denlinger et al., 2016; Murdoch et al., 2012).

Vitamin D and Community-Acquired Pneumonia

Community-acquired pneumonia is another infectious disease, caused most often by bacteria. The most important risk factors include: advanced age, chronic lung disease (especially COPD), smoking, immunosuppression, and aspiration risk. A meta-analysis by Zhou et al., (2019) found a significant association between low serum vitamin D levels (<20 ng/mL) and increased risk of community-acquired pneumonia (CAP) (OR = 1.64; 95% CI: 1.00–2.67). In critically ill patients, particularly those with severe pneumonia or sepsis, vitamin D levels are markedly reduced and correlate with clinical outcomes and prognosis (De Pascale et al., 2016; Lu et al., 2018). Lung epithelial cells convert inactive vitamin D into its active form during pulmonary infections, increasing the expression of cathelicidin and thereby enhancing the host's ability to combat infection - especially Pseudomonas Aeruginosa and Streptococci (Gunville et al., 2013). Moreover, vitamin D deficiency is directly associated with impaired lung function and represents an independent risk factor for the development of pneumonia (Lambert et al., 2014). Therefore, vitamin D status influences not only the incidence of respiratory diseases but also the severity of CAP. Vitamin D supplementation may help reduce both the risk of disease and its clinical severity.

Vitamin D and UTI

Urothelial barrier function depends largely on tight junction proteins, which regulate paracellular permeability and create a protective barrier against invading pathogens, as described above in section 3.4. These proteins are located at the junction of apical and lateral membranes of urothelial cells, ensuring adhesion between neighboring epithelial cells. In the study of Mohanty et al., (2020) it was demonstrated for the first time that vitamin D induces tight junction proteins in the urinary bladder during Escherichia coli infection. In the blood-brain barrier, similar effects have been observed - vitamin D deficiency reduces occludin and claudin-5 expression, which causes worsening of blood vessel tightness and durability (Sayeed et al., 2019).

According to a study, it was found that occludin and claudin-14 expression occur primarily in superficial (umbrella) cells of the bladder in both humans and mice, with lower expression in basal layers (Mohanty et al., 2020). This pattern aligns with earlier studies showing specific localization of tight junction proteins across species - for example, occludin, claudin-8, and claudin-12 at apicolateral junctions, and claudin-4 at basolateral membranes (Acharya et al., 2004). Disruption of tight junctions increases epithelial permeability and makes microbial invasion much more rapid. Uropathogenic E. coli, through disruption of ZO-1, may also impair the urothelial barrier, which vitamin D may prevent. However, supplementation in vitamin D-deficient mice shows limited effects on some junction proteins despite reducing inflammation via vitamin D receptor signaling (Gorman et al., 2017). Vitamin D also stimulates antimicrobial peptide production in the bladder, skin, and intestines. The conclusion of the listed UTIs studies is that supplementation of vitamin D may help to prevent bacterial invasion in postmenopausal women.

To summarize the above-mentioned clinical studies evaluating the relationship between vitamin D supplementation and respiratory tract infections, the findings are presented in Table 2.

Table 2. Vitamin D supplementation and respiratory infections - clinical studies.

Author (year)	Population	Study design	Vitamin D dose	Duration	Outcome
Martineau et al., (2017)	Mixed populations	Meta-analysis (IPD)	Various	Various	↓ risk of acute respiratory infections (strongest in deficient individuals)
Murdoch et al., (2012)	Healthy adults	RCT	100,000 IU monthly	18 months	No significant effect on URTI incidence

Urashima et al., (2010)	Schoolchildren	RCT	1200 IU/day	4 months	↓ influenza A incidence
Li-Ng et al., (2009)	Adults	RCT	2000 IU/day	12 weeks	No significant reduction in URTI
Camargo et al., (2012)	Children (Mongolia)	RCT	300 IU/day (via milk)	7 weeks	↓ acute respiratory infections
Denlinger et al., (2016)	Asthma patients	RCT	4000 IU/day	28 weeks	No reduction in colds
Bergman et al., (2015)	Patients with frequent RTIs	RCT (post hoc)	4000 IU/day	1 year	Improved well-being, ↓ infections

Current Recommendations and Clinical Practice

Having established the importance of vitamin D in immune processes, it is essential to consider the scale of vitamin D deficiency in modern industrialized societies. In Central Europe, as well as in much of Western Europe, cutaneous synthesis of vitamin D occurs mainly between May and September; therefore, seasonal or year-round supplementation with cholecalciferol is firmly recommended. Age, body weight, lifestyle, and sun exposure should all be considered when determining the appropriate vitamin D dosage, as shown in recommendations published in 2023 by a Polish expert panel. Vitamin D_3 is the first option when treating or preventing vitamin D deficiency. Calcifediol may also be used, but in more specific clinical circumstances (Płudowski et al., 2023). Prophylactic doses vary by age. In infants the proper dosage is 400 IU (10 μg) per day, then up to 600IU/day in the second half of infancy. In children aged 1–10 years, 600–1000 IU/day is recommended, usually throughout the year. For people aged 15 to 65, recommended supplementation doses are wide, ranging from 800 to 2000 IU/day depending on sun exposure (Płudowski et al., 2023).

In individuals over 65 years of age and in patients with obesity, even higher doses (typically 2000–4000 IU/day) are recommended. It's because of reduced cutaneous synthesis and increased sequestration in adipose tissue. In these groups, supplementation plays an important role in preventing osteoporosis. In clinical practice, assessment of serum 25-hydroxyvitamin D [25(OH)D] concentration is a well-known component of management. Serum levels above 20 ng/mL are generally sufficient, while values in the range of 35–50 ng/mL are, according to a study, considered optimal (Pietras et al., 2009). In cases of confirmed deficiency, higher therapeutic doses are used initially, followed by maintenance therapy. In the general population, it's not particularly recommended to measure vitamin D levels, but in a little more specific group, namely, people suffering from osteoporosis or immunosuppressed patients. Excessive supplementation inevitably leads to hypercalcemia, which may manifest as chronić or acute kidney damage, intestinal disturbances of various severity – from mild stomach pain to severe paralytic ileus. Therefore, doses exceeding 4000 IU/day should be used with caution and preferably under medical supervision (Zittermann et al., 2023). Taking individual risk factors into consideration remains the most important point of proper vitamin D dosage adjustment.

4. CONCLUSION

A proper vitamin D level is beneficial for both innate and adaptive immunity, as demonstrated in clinical and in vitro studies. Observational data suggest an association between vitamin D deficiency and increased susceptibility to infections. Determining vitamin D levels and supplementing its deficiency in hospitalized patients with a severe course of certain infectious diseases seems to be a logical therapeutic step. Yet, final clinical confirmation remains uncertain and assessment of vitamin D3 level remains a relatively expensive procedure compared to other tests. Maintaining adequate vitamin D levels, however, is a safe, relatively easy and potentially beneficial strategy, particularly in high-risk populations. Further randomized controlled trials are required to determine its clinical relevance in the prevention and management of infectious diseases.

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Authors' Contributions

AK conceived the study and drafted the manuscript. MK, SP, and AD contributed to data analysis and literature review. KK, MJ, NK, DS, MM, and JK participated in manuscript revision. All authors approved the final version of the manuscript.

Informed consent
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Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

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Data and materials availability
All data associated with this study will be available based on the reasonable request to corresponding author.

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