The Case for Vitamin D Supplementation to Improve Protection against Respiratory Tract Infections

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Abstract: Background: An adequate vitamin D status is essential for normal immune function. Vitamin D sub-nutrition is widespread, especially in low sunlight regions and in certain high-risk groups. There is growing evidence that vitamin D supplementation can reduce the risk of infection of the respiratory tract.

Objective: The aim was to review the mechanisms whereby vitamin D supports the chemistry of optimal innate and adaptive immunity, and to evaluate critically the current evidence for the use of vitamin D supplements to help to minimize respiratory infection risk, particularly in individuals with sub-optimal vitamin D plasma levels.

Method: PUBMED and MEDLINE were searched using the terms: vitamin D; cholecalciferol; calcitriol; calcifediol; respiratory infections; influenza; pneumonia; respiratory syncytial virus, respiratory tract infection; chronic obstructive pulmonary disease (COPD); immunisation; vaccination; innate immunity; adaptive immunity. Papers for citation were selected by the authors on the basis of quality and relevance.

Findings: Vitamin D is needed for optimal function of innate and adaptive immune systems. The evidence for a protective effect of vitamin supplementation is the strongest for viral infection, particularly in people with plasma calcifediol levels below 25 nmol/L. However, the role of vitamin D in influenza risk and as an adjunct to influenza immunization is not clear. There is some evidence that a sufficient vitamin D status reduces the risk of infective exacerbations of COPD, and probably helps in the defence against some bacterial infections of the respiratory tract.

Conclusion: Individuals with vitamin D deficiency have enhanced protection against some respiratory infections when given supplements. There are also other benefits including improved bone and muscle function, and mood. Further research is needed to identify sub-groups most likely to benefit from supplements.

Keywords: Chronic obstructive pulmonary disease, immune function, influenza, respiratory tract infection, viral infection, vitamin D supplementation, vitamin D.

1. INTRODUCTION

The health benefits of sunlight have been observed since ancient times. For example, Hippocrates included exposure to the sun in his regimen for the treatment of phthisis (tuberculosis) in the 5th century BCE [1]. More recently, sunlight and cod liver oil were used with apparent good effect as adjunctive treatments in sanatoria for tuberculosis in the 19th century CE [2]. Though the role of sunlight, and indeed cod liver oil, in these contexts is complex, the most obvious common factor is vitamin D. The critical roles of vitamin D in the conservation of health have gradually come to light in recent decades, beginning with its identification, structural definition, synthesis and physiology, alongside the vital part it plays in calcium homeostasis and the normal formation and structural maintenance of bone [3]. However, vitamin D is now understood to have a number of other important physiological functions, most clearly in immune function, muscle function and mood stability [3-6]. Of growing interest is its effect in the defence against common respiratory pathogens, particularly viruses. It is that aspect of vitamin D deficiency and supplementation that will be the focus of this paper.

2. SEARCH METHODS

We searched PUBMED and MEDLINE using various combinations of the following terms: vitamin D;
cholecalciferol; calcitriol; calciifiedol; respiratory infections; influenza; pneumonia; respiratory syncytial virus, respiratory tract infection; chronic obstructive pulmonary disease; immunisation; vaccination; innate immunity; adaptive immunity for the period 1998-2018. Because of the diverse nature of the extant literature in this field we conducted a topic review rather than a formal systematic review. Around 300 papers were identified in abstract form by the initial search, from which 90 were deemed by the authors to be of sufficient quality for reading in depth. Those chosen for citation were selected by the authors on the grounds of relevance to the topic and scientific credibility. Some other papers and sources have been included in the reference list to support the clinical context and historical perspective of the review.

3. VITAMIN D SOURCES AND CHEMISTRY

For healthy humans living at the full range of latitudes, the primary source of vitamin D is through photosynthesis from precursors in skin. Ultraviolet B in sunlight converts endogenous 7-dehydrocholesterol to cholecalciferol in the epidermis. This is then hydroxylated to calciifiedol (25-hydroxycholecalciferol) by liver cells, then hydroxylated again to calcitriol (1,25-dihydroxycholecalciferol), the active form of vitamin D, by renal cells [7]. Alternatively, calcitriol can be supplied in natural dietary sources, such as fish, eggs and dairy products, and in foods fortified during manufacture. Calciifiedol and calcitriol can also be given as medicines in tablet form.

4. THE IMMUNE FUNCTION OF VITAMIN D

The most completely delineated function of vitamin D is the key role it plays in calcium homeostasis, whereby alongside parathyroid hormone and calcitonin it controls the intestinal absorption and renal reabsorption of calcium, and bone turnover through an influence on osteoclast activity [8]. An understanding is emerging of the equally important but considerably more complex contribution made by vitamin D to the integrity of immune function in both innate and adaptive immune systems. In this review we will consider that contribution at three main levels. First, the discovery that a range of immune competent cells can synthesize calcitriol. Second, the function of vitamin D receptors (VDRs) on immune cell membranes. Third, the function of vitamin D in the regulation and modulation of immune systems.

Cells involved in both innate and adaptive immunity contain the enzyme CYP27B1 (1-alpha-hydroxylase) in their mitochondria and are therefore an extrarenal source of active calcitriol, though the effect is probably mainly intracellular. The same range of cells, including macrophages, neutrophils, dendritic cells, natural killer cells, B cells, CD4 and CD8 cells, also have surface VDRs [9]. The expression of CYP27B1 and VDRs is dynamic in response to the presence of antigens and certain cytokines. For example, CYP27B1 is upregulated by paracrine secretion of interleukin-15 (IL-15) and interferon-gamma (IFN-g) when Gram positive bacteria or Mycobacteria bind with toll-like receptors on macrophages [10]. By binding with VDRs, calcitriol regulates local immune function through intracrine, paracrine and autocrine mechanisms that influence gene transcription. For example, transcription occurs for the production of the anti-microbial peptide cathelicidin, which encourages bacterial death by the formation of autophagosomes or autophagy [9]. Similarly, transcription for the upregulated release of beta defensin, a peptide that has a positive chemotactic effect on mast cells and memory T lymphocytes and activates dendritic cells [11]. Calcitriol also has a broader effect by modulating the secondary expression of a number of genes responsible for the transcription of pro-inflammatory cytokines [10]. Further, through CYP27B1 expression and VDR activity, calcitriol appears also to have immune down-regulating properties, suggesting a critical role in the modulation of overall immune responses, including timely pro-inflammatory defensive activity and the prompt return to the immune baseline. The controlling effect of calcitriol on tolerogenic dendritic cell maturation and antigen handling [12], the downregulation of pro-inflammatory cytokine production and upregulation of anti-inflammatory cytokine release by CD4 cells are further examples of this modulatory effect [9, 13]. By a similar mechanism regulatory T cell function is enhanced [14, 15], and the intracellular inactivation of vitamin D in response to rising anti-inflammatory interleukin-4 (IL-4) and falling IFN-g are considered to be evidence of a local modulatory mechanism to minimise inflammatory damage [10]. A subtle effect of calcitriol on plasma cells and B cells has also been observed whereby, in the post-infected stage, the production of new plasma cells is lowered but long-term function of existing plasma cells is retained. This has been interpreted as a beneficial effect of vitamin D in preserving the protective role of immune memory while avoiding the potential damage of a hyper-immune state [9]. These immune functions of vitamin D have implications not only for infection but also a wide range of immune disorders, including for example, asthma, allergy and auto-immune diseases, and the effects of maternal deficiency on neonatal immunity. A full review of that whole spectrum is outside the scope of this paper which is primarily focused on infection.

5. VITAMIN D DEFICIENCY: DEFINITIONS AND EPIDEMIOLOGY

Vitamin D status is normally determined by measuring the plasma concentration of calciifiedol (25-hydroxycholecalciferol). In the United Kingdom (UK) a plasma level of < 25 nmol/L is defined as deficient, mainly due to the increased risk of rickets (children) and osteomalacia (adults). That definition has become the subject of debate in the light of an increasing body of evidence of adverse effects on immune function, muscle function and mood at plasma levels above 25 nmol/L. The Institute of Medicine dietary reference committee considers < 30 nmol/L to be deficient, 30-50 nmol/L to be inadequate and > 50 nmol/L to be sufficient [16]. Further, the European Task Force on vitamin D defines deficiency as < 50 nmol/L, with 52-72 nmol/L considered inadequate and > 75 nmol/L sufficient [17]. The main factors contributing to vitamin D
deficiency are low sunlight exposure, particularly for those with darker skin, a need to wear clothes that cover almost all skin, and inability to venture outdoors due to immobility or frailty. These effects are exaggerated at high latitude. An overview of vitamin D status in the UK concluded that insufficiency is widespread, with 20 per cent of children and adults defined as deficient and 60 per cent as inadequate [18]. At age 64 years, 10 percent of functionally independent people and 40 per cent of those in institutional care or housebound were deficient [19, 20]. Even in the summer months people over the age of 85 years living in the city of Newcastle-upon-Tyne fell in the range 27-45 nmol/L and therefore had deficient or inadequate vitamin D status by prevailing definitions [21]. These findings are not confined to the United Kingdom but have been confirmed in other northerly countries, including the United States of America (USA) [22].

6. VITAMIN D DEFICIENCY: RISK OF INFECTION

A large population study in the USA found that after adjusting for multiple variables, adults who had a plasma calcifediol level of < 45 nmol/L had a significantly increased risk of hospitalization for respiratory infection compared to those with levels > 75 nmol/L (relative risk 2.8, p < 0.01) [22]. A similar UK cross-sectional study showed that every 10 nmol/L increase in plasma calcifediol was associated with a 7 per cent reduction in the risk of respiratory tract infection [23], and supplementing with vitamin D to achieve an average rise of 25 nmol/L resulted in a fall in the rate of upper respiratory infection (URTI) to a relative risk of 0.91 [24]. Plasma vitamin D levels have also been shown to correlate negatively with the severity of lower respiratory tract infection (LRTI) in children [25], and the rate of hospitalization for that condition [26]. A supplementation study also showed not only an approximate halving of the URTI rate, but also a significant fall in absence from work [27]. Such an effect on behaviour might not be solely due to immune system function and could be at least partly the result of improved mood. Though the prevalence of vitamin D insufficiency is higher in low sunlight regions [21, 22] there have been no credible studies comparing the rates of respiratory infection between high and low sunlight regions. The main difficulty in interpreting such studies lies in differing patterns of viral and bacterial epidemiology, housing density, general nutrition and opportunities for ease ascertainment in differing geographical locations.

Patients attending ear-nose-throat outpatient clinics for infection-related conditions have been found to have a higher incidence of vitamin D deficiency compared to the general population, suggesting a causal link [28], and children with recurrent tonsillopharyngitis were found to have significantly lower plasma calcifediol levels compared with healthy age-matched controls [29]. Further, adults with streptococcal tonsillopharyngitis who had plasma calcifediol levels < 20 nmol/L had a significantly higher risk of recurrence (risk ratio 1.61, p < 0.001) [30]. Most of these studies were observational and were conducted on small numbers and few included an investigation of the effects of vitamin D supplementation, so some caution is needed in drawing conclusions. This uncertainty paved the way for the large meta-analysis described in the next paragraph.

7. VITAMIN D SUPPLEMENTATION

7.1. The Effect on Acute Respiratory Infection Rates in Adults

A recent meta-analysis of 25 randomized controlled trials that included a total of 10,993 patients found that vitamin D supplementation had a protective effect against acute respiratory infection (odds ratio 0.88, p=0.003), with an overall number needed to treat (NNT) of 33 to prevent 1 episode per year. Moreover, in patients with pre-supplement plasma calcifediol levels < 25 nmol/L, the effect was more pronounced (odds ratio 0.58, p=0.002, NNT=8). The dose pattern also influenced the outcome, with those receiving daily or weekly supplements showing greater protection than those given single boluses (odds ratio 0.81, p<0.001, NNT=20). This finding was particularly strong for patients with pre-supplement plasma calcifediol levels of < 25 nmol/L (odds ratio 0.30, p<0.001, NNT=4), in whom bolus dosing conferred no significant protection. Interestingly, weekly or daily vitamin D supplements were also protective in those with initial plasma levels > 25 nmol/L (odds ratio 0.75, p=0.006). No serious adverse effects were recorded for people receiving a vitamin D supplement [31]. This meta-analysis is arguably the best extant evidence for the beneficial effect of vitamin supplementation in reducing the risk of respiratory infection. Of course, it is likely that other benefits were conferred, such as reduction of other infections, improved muscle function and better mood, though those outcomes were not considered in most of the studies included in the meta-analysis. Other evidence is corroborative. For example, people above the age of 70 years receiving vitamin D supplementation have been found to have significantly fewer antibiotic prescriptions for URTI compared to those given a placebo (relative risk 0.53, p=0.02) [32]. Overall, it appears that people with low plasma vitamin D levels have the clearest benefit in this context, which has led some authors to advocate testing for vitamin D status before prescribing supplements [33]. There is less evidence regarding the influence of vitamin D status on mortality in patients with severe LRTI. A study conducted in patients with community-acquired pneumonia found significantly higher episode mortality in patients with clearly deficient levels (hazard ratio 1.91, p=0.031), and survivors had a higher 5-year mortality [34]. However, the difference was likely to be a least partly due to frailty and complex comorbidities.

7.2. Influenza

The role of vitamin D status in influenza risk has not been clearly determined. A seasonal variation in vitamin D status is seen in countries of high latitude due to lower rates of skin photosynthesis in winter months. It has been proposed that low population vitamin D levels could act as a trigger factor for seasonal influenza epidemics [35, 36]. Nasopharyngeal swabs were found to be less often positive for influenza A antigens in children taking vitamin D supplements [35] and adults taking a supplement were found to self-report influenza symptoms less frequently, though
microbiological diagnostic confirmation was not included [36]. Neither of those studies measured initial vitamin D status, and co-morbid conditions that might have had a complex influence were not taken into account. Most published studies in this domain have not shown a clear benefit from vitamin D supplementation, though most have methodological flaws or are underpowered and are therefore not cited in this paper. One well-conducted trial of supplementation given to healthy subjects of high school age during an influenza H1N1 epidemic demonstrated no overall reduction in the incidence of confirmed influenza during a two-month period [37].

The effect of vitamin D supplements on the efficacy of influenza vaccines is also not clear. As discussed in the paragraphs above vitamin D has an immunomodulatory role in the innate and adaptive immune systems, both of which are involved with successful vaccination, and in animal studies the adjunctive local administration of calcitriol with influenza vaccine produced an enhanced mucosal and systemic antibody response [38]. It seems logical, therefore, to anticipate that ensuring a replete vitamin D status would measurably improve vaccine performance. However, in the few human studies that have been conducted the findings have varied. Most recent studies, including those consolidated into a meta-analysis, have been inconclusive or have not demonstrated a relationship between vitamin D status and response to influenza immunisation [39].

7.3. Chronic Obstructive Pulmonary Disease (COPD)

COPD is a common and increasingly prevalent cause of morbidity and premature mortality worldwide. Individuals with COPD are at higher risk of having an insufficient vitamin D status than the general population for a number of reasons, including decreased photosynthesis resulting from skin changes related to smoking and ageing, spending less time outdoors due to reduced exercise tolerance and impaired mobility, and metabolic changes consequent upon the therapeutic use of systemic corticosteroids that lead to enhanced vitamin D degradation and lower storage capacity [40]. A probable contributing factor is a diet poor in vitamin D associated with low income, and, in some patients, impaired appetite. Studies of vitamin D status in people with COPD have shown a prevalence of an insufficient or overtly deficient state in 31-77 per cent, and an association between low plasma vitamin D levels and the risk of infective exacerbations has been observed, though cause and effect has not been proven [22, 41, 42]. The rate of decline of lung function in COPD does not appear to be related to vitamin D status [43], though care must be exercised in interpreting that finding as there has been no extended longitudinal study of the relationship. Further, there is no evidence that vitamin D supplementation improves lung function in COPD, but in one study a significant improvement in symptoms and performance was observed [44], possibly through an immune modulatory mechanism through enhanced anti-inflammatory IL-4 production and consequent damping of airway inflammation, though this effect has been most clearly demonstrated in asthma [45].

The role of vitamin D in infective exacerbations of COPD (IECOPD) is to some extent clearer. IECOPD present a considerable burden on individual patients and health services, particularly when in the moderate-severe category [46]. The question has therefore arisen as to whether the immune function properties of vitamin D could have a preventative or ameliorating effect in IECOPD. Patients with plasma calcifediol levels < 25 nmol/L were found to be of greatly increased risk of one-time IECOPD and of hospitalisation (odds ratio 30.5, p<0.001, and 3.83, p=0.02 respectively), while for recurrent IECOPD and hospitalisation the odds ratio was 18.1 (p=0.001) and 4.57 (p=0.001) respectively [47]. More importantly from the perspective of clinical utility, it has been shown that supplementation of COPD patients with plasma calcifediol levels < 50 nmol/L reduced the risk of moderate-severe exacerbations (hazard ratio 0.57, p=0.021) [48]. It has been suggested that the observed benefit could be vitamin D-mediated enhanced synthesis of antimicrobial cytokines, such as IL-37, and improved performance of other local components of the innate immune system [48]. On balance, it appears prudent to ensure an adequate vitamin D status in patients with COPD. Benefits include some apparent protection from IECOPD and the overall weight of evidence indicates a reduced risk of other infections. Further, patients with COPD tend towards frailty and therefore also stand to gain from the other beneficial effects of being replete for vitamin D, including bone health, muscle function and mood [3-6].

7.4. Other Respiratory Infections

Bronchiolitis, which is primarily caused by infection with respiratory syncytial virus (RSV), tends to occur in yearly epidemics mainly in children below the age of 2 years. A substantial proportion of patients need treatment in hospital and the condition can be fatal. Laboratory studies have indicated that vitamin D reduces cytokine-mediated inflammatory damage to RSV-infected bronchial epithelial cells [49]. Also, it has been found that children with specific VDR polymorphisms are at increased risk of bronchiolitis [50]. Some studies have found a link between low vitamin D status and the severity of lower respiratory tract infections in children [51, 52], though a large Canadian study found no link between plasma vitamin D levels and the risk of hospitalisation for respiratory infection in children [53]. On the other hand, a study of neonates found that infants with low umbilical cord plasma calcifediol levels had a higher incidence of LRTI, mainly bronchiolitis, in the first 2 years of life [54]. Similarly, a study of bronchiolitis risk up to the age of 1 year found significantly lower risk in children with cord blood vitamin D levels in the sufficient range [55]. One survey found that of neonates admitted to intensive care for LRTIs, 87.5% had plasma calcifi ediol levels < 20 nmol/L, as did 67.5% of the mothers [56]. Umbilical cord vitamin D level is, of course, a reflection of maternal vitamin D status and could be an indicator of other nutritional and socio-economic factors that might adversely affect infection risk, so caution is needed in interpreting these findings as firm evidence of a direct link between vitamin repletion and infection risk in young children.

There is some evidence for the role played by vitamin D in other infections of the respiratory system. Patients with bronchiectasis who were found to be vitamin D deficient had
a higher prevalence of chronic colonisation with Pseudomonas aeruginosa or Haemophilus influenzae leading to recurrent infective exacerbations [57]. They also had a higher rate of decline in lung function and lower quality of life scores when compared to patients with levels in the insufficient and sufficient ranges. Again, this does not prove cause and effect, though it is consistent with other findings and the core contention that adequate vitamin D nutrition supports normative immune function and contributes to protection against infection. The evidence for the influence of vitamin D deficiency on predisposition to other infections of the respiratory tract is building steadily and generally indicates that deficient individuals are at greater risk, and that supplementation reduces risk. A meta-analysis concluded that vitamin D deficiency was more likely to be a risk for pulmonary tuberculosis rather than a consequence of the disease [58]. On the other hand, 3 large independent studies have shown that vitamin D supplementation had no preventive effect on the risk of pneumonia in adults or children [59]. Vitamin D supplementation probably helps to protect cystic fibrosis patients colonised by Aspergillus from detrimental IL-13 mediated immunoglobulin-E responses, probably through an immune modulating mechanism [60].

8. DISCUSSION

The current state of the evidence supports an emerging view that people with overt vitamin D deficiency have impaired immune function and are at risk from various forms of infection. The clearest evidence pertains to viral infections, particularly of the respiratory tract, though there is probably an increased susceptibility to bacterial infection in deficient individuals. A lack of certainty about what constitutes an inadequate, but not definitely deficient, vitamin D status has probably inhibited a clear interpretation of the impact of marginal vitamin sub-nutrition on immune function and the consequent risk of infection. That factor has also rendered the issue of supplementation more complex as a research subject. Nevertheless, it is broadly accepted that a large section of the population in areas of low sunlight has less than optimal vitamin D plasma levels. Further, there is persuasive evidence that supplementation reduces the risk of respiratory infection in people with deficient and sub-optimal plasma vitamin D levels, and is also probably effective to some extent in apparently replete individuals. It seems likely that further progress with untangling the complex relationship between vitamin D, immune function and protection against infection will depend on developing a greater understanding of the biochemical mechanisms involved, a more sophisticated and contextualized definition of vitamin D deficiency, and further adequately powered and carefully designed research trials.

CONCLUSION

This review has summarized the evidence for the role of vitamin D in respiratory infection. The complex influence of vitamin D on innate and adaptive immune responses and modulation is becoming apparent. The overall indication is that vitamin D deficiency impairs some aspects of immunity and predisposes to certain respiratory infections, and that supplementation can be protective in some circumstances, particularly for overtly deficient individuals. However, the case for general supplementation as prophylaxis against respiratory infection is not clear and can probably only be supported in high risk groups. Further, excessive supplementation can lead to vitamin D toxicity, though that is very unlikely to occur at normative daily doses [61]. Clinical supervision based on current guidelines is recommended, and prolonged high dose self-medication should be discouraged [62]. Many of the existing studies of the efficacy of vitamin D in reducing infection risk have methodological weaknesses, including small size, lack of stratification, mixed outcome definitions and variable supplementation regimens. Therefore, controlled intervention studies of high quality are needed to clarify the position further.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES


Lanham-New SA, Buttriss JL, Miles LM, Jat KR. Vitamin D deficiency and lower respiratory tract infections.


