

Vitamin D in respiratory diseases

A Goolam Mahomed, MB BCh, FCP(SA), FCCP

Department of Intensive Care, Sefako Makgatho Health Sciences University, Pretoria, South Africa

Corresponding author: A Goolam Mahomed (akhtergm@telkomsa.net)

Vitamin D has traditionally been known for its role in bone homeostasis with its effects on calcium and phosphate absorption and secretion. However, new evidence is emerging of its effects on a number of other cells, especially the immune system. This article reviews the role of vitamin D as it pertains to the respiratory tract and respiratory diseases.

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Vitamin D belongs to a group of fat-soluble secosteroids and is required for intestinal absorption of calcium (Ca^{2+}) and phosphate (PO_4^{3-}). In humans, vitamin D is present as ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3), and both forms can be ingested from the diet and/or supplements. The body can also synthesise vitamin D from cholesterol when sun exposure is adequate, hence it has been nicknamed the 'sunshine vitamin'.^[1] Recently, interest has grown in the role of vitamin D in many non-skeletal medical conditions, including respiratory infection and lung function.^[2] Emerging evidence indicates that vitamin D-mediated innate immunity is important in host defences against respiratory tract pathogens.^[3] Observational studies suggest that vitamin D deficiency increases the risk of respiratory infections, incident wheezing illness in children and adults, and can cause asthma exacerbations. Vitamin D also modulates regulatory T-cell function and interleukin-10 (IL-10) production, which may increase the therapeutic response to glucocorticoids in steroid-resistant asthma.

History

In 1914, American researchers McCollum and Davis discovered a substance in cod liver oil which was later called 'vitamin A'. In 1922, McCollum tested modified cod liver oil in which the vitamin A had been denatured. The modified oil cured rickets in sick dogs, so McCollum concluded the factor in cod liver oil that cured rickets was distinct from vitamin A. He called it vitamin D because it was the fourth vitamin to be named.^[4] In 1923, American biochemist Harry Steenbock demonstrated that the irradiation of foodstuffs, especially milk, led to a cure for rickets. In 1932, an academic collaboration between Bourdillon, Rosenheim, King and Callow led to the isolation and characterisation of vitamin D and later in the 1930s, Windaus further clarified the chemical structure of vitamin D. By 1972, Holick had discovered that vitamin D was metabolised to two active forms, i.e. calcidiol and calcitriol.^[5,6]

Recommended dietary allowance of vitamin D

The US Institute of Medicine (IOM) recommended dietary allowance of vitamin D is 400 international units (IU) per day for children younger than 1 year of age, 600 IU per day for children at least 1 year of age and adults up to 70 years, and 800 IU per day for older adults.

The US IOM concluded that serum 25-hydroxyvitamin D (25(OH)D) of 20 ng/mL or more would cover the requirements of 97.5% of the population.^[7] The US Endocrine Society's Clinical Practice Guidelines suggest that 400 - 1 000 IU/day may be needed for children aged <1 year, 600 - 1 000 IU/day for children aged ≥ 1 year, and 1 500 - 2 000 IU/day for adults aged ≥ 19 years to maintain 25(OH)D above the optimal level of 30 ng/mL.^[8]

Sources of vitamin D

Sources of vitamin D include sun exposure, diet and supplements. Vitamin D_2 is obtained from ultraviolet irradiation of the yeast sterol, ergosterol, and remains the only pharmaceutical form of vitamin D approved by the US Food and Drug Administration. Vitamin D_3 is synthesised in the skin and is present in oil-rich fish such as salmon, mackerel and herring. Both vitamin D_2 and vitamin D_3 are used in food fortification and supplements. The major foods fortified with vitamin D (D_2 or D_3) are milk, yoghurts, cheeses, orange juice and cereals. Vitamin D is metabolised in the liver to 25-hydroxyvitamin D_3 (25(OH) D_3), which is the best available indicator of vitamin D status. In the kidneys, 25(OH) D_3 is metabolised to its active form, 1,25-dihydroxyvitamin D_3 , (1,25(OH) $_2\text{D}_3$). The levels of 1,25(OH) $_2\text{D}_3$ do not reflect vitamin D status as they are regulated by parathyroid hormone, Ca^{2+} and PO_4^{3-} levels, and fibroblast growth factor 23.^[7,8]

Physiology of vitamin D

Intestinal Ca^{2+} and PO_4^{3-} absorption is regulated by 1,25(OH) $_2\text{D}_3$, and with severe vitamin D deficiency the efficiency of Ca^{2+} absorption decreases from 30 - 40 to 10 - 15%. Vitamin D deficiency also stimulates the parathyroid glands, leading to secondary hyperparathyroidism. Secondary hyperparathyroidism maintains serum Ca^{2+} in the normal range at the expense of mobilising Ca^{2+} from the bone, and increases urinary PO_4^{3-} loss, resulting in a decrease in serum PO_4^{3-} level and an inadequate calcium-phosphate product ($\text{Ca}^{2+} \times \text{PO}_4^{3-}$). This results in a defect in bone mineralisation, which leads to rickets in children and osteomalacia in adults.^[7,8]

Non-skeletal actions of vitamin D

The lung, brain, prostate, breast and colon tissues, among others, as well as immune system cells, express the vitamin D receptor (VDR) and responds to 1,25(OH) $_2\text{D}_3$, the active form of vitamin D, which

is the ligand for the VDR receptor. In fact, cells without the VDR receptor are rare. In addition, some of these tissues and cells express the enzyme 25-hydroxyvitamin D-1 α -hydroxylase, which is encoded by the *CYP27B1* gene. Binding of 1,25(OH) $_2$ D $_3$ to the VDR leads to the formation of a heterodimer with retinoid X receptor, which combines with vitamin D response elements (VDREs) that then regulate gene expression.^[9] Directly or indirectly, 1,25(OH) $_2$ D $_3$ controls >200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis and angiogenesis. It decreases cellular proliferation of both normal and malignant cells, and induces their terminal differentiation.^[3] One practical application is the use of 1,25(OH) $_2$ D $_3$ and its active analogues for the treatment of psoriasis.^[2] 1,25(OH) $_2$ D $_3$ is also a potent immunomodulator. Monocytes and macrophages exposed to a lipopolysaccharide or to *Mycobacterium tuberculosis* up-regulate the VDR gene and the 25-hydroxyvitamin D-1 α -hydroxylase gene. Increased production of 1,25(OH) $_2$ D $_3$ results in synthesis of cathelicidin, a peptide capable of destroying *M. tuberculosis* as well as other infectious agents. When serum levels of 25(OH)D $_3$ fall below 20 ng/mL (50 nmol/L), the monocyte or macrophage is prevented from initiating this innate immune response.^[3] 1,25-(OH) $_2$ D $_3$ also inhibits renin synthesis, increases insulin production and increases myocardial contractility.^[2]

Asthma and vitamin D levels

The majority of studies report an inverse association between serum 25(OH)D $_3$ levels and asthma morbidity.^[9] Vitamin D may play a causal role in asthma pathophysiology and vitamin D status may also impact on asthma therapy via a number of mechanisms, which include its antiviral properties, enhanced steroid responsiveness and down-regulation of atopy. It may also influence asthma by regulating the expression of disease-susceptibility genes. Biologically, there are data to suggest that 1,25(OH) $_2$ D $_3$ can directly enhance secretion of the anti-inflammatory molecule IL-10 from regulatory T-cells derived from steroid-resistant individuals with asthma.^[3] In vitro, 1,25(OH) $_2$ D $_3$ regulates inflammatory responses in airway epithelial cells and airway smooth muscle cells, both of which may be targets of corticosteroid therapy.^[3]

The role of maternal vitamin D levels and their association with childhood wheeze and atopy is somewhat controversial. Hypponen *et al.*^[10] found that vitamin D supplementation increased the risk of asthma in Finnish infants, but many recent studies have come to different conclusions. Wills *et al.*^[11] found no evidence that maternal levels of vitamin D correlate with childhood atopy or asthma, but the Vitamin D Antenatal Asthma Reduction Trial (VDAART) study found that vitamin D supplementation during pregnancy led to decreased levels of asthma and wheezing.^[12] In the Generation R Study, Gazibara *et al.*^[13] found that maternal vitamin D levels did not correlate with asthma, but low levels of 25(OH)D $_3$ at birth in infants were associated with higher airway resistance in childhood. In a recent meta-analysis of 15 prospective studies, Song *et al.*^[14] suggested there may be a U-shaped association between maternal 25(OH)D $_3$ levels and asthma, with the lowest risk of asthma at approximately 70 nmol/L of 25(OH)D $_3$.

In the HUNT study of a cohort of 25 616 Norwegian adults, the authors showed that low vitamin D status was not significantly associated with incident asthma in most adults, but it may have increased risk in men without allergies.^[15] In contrast, Korn *et al.*^[16]

found that vitamin D deficiency and insufficiency were clearly associated with asthma, and also with poor control of asthma. A number of recent trials using vitamin D replacement therapy did not show improvement in asthma control. The Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma (VIDA) trial studied adult patients with symptomatic asthma and a serum 25(OH)D $_3$ level of <30 ng/mL across nine academic medical centres in the USA. Oral vitamin D $_3$ (100 000 IU once, then 4 000 IU/day for 28 weeks; $n=201$) or placebo ($n=207$) was added to inhaled ciclesonide (320 μ g/d). Vitamin D $_3$ did not reduce the rate of first treatment failure or exacerbation in adults with persistent asthma and vitamin D insufficiency.^[17] Similarly, a trial of bolus-dose vitamin D $_3$ supplementation did not influence exacerbation time for asthma or upper respiratory tract infections (URTIs) in adults with vitamin D deficiency.^[18] A Cochrane meta-analysis recently showed that vitamin D supplementation does reduce the risk of severe exacerbations, and improves asthma symptom control in people with mild to moderate asthma.^[19]

Vitamin D and chronic obstructive pulmonary disease

Low serum 25(OH)D $_3$ levels have been associated with lower forced expiratory volume in 1 second (FEV $_1$), impaired immunological control, and increased airway inflammation.^[20,21] Many patients with chronic obstructive pulmonary disease (COPD) have a vitamin D deficiency, and therefore the effects of vitamin D supplementation may extend beyond preventing osteoporosis. In a recent study to determine if baseline 25(OH)D $_3$ levels relate to subsequent acute exacerbation of COPD (AECOPD) in a cohort of patients at high risk for AECOPD, plasma 25(OH)D $_3$ was measured at baseline in 973 participants on entry into a 1-year study designed to determine if daily azithromycin decreased the incidence of AECOPD. Relationships between baseline 25(OH)D $_3$ and AECOPD over 1 year were analysed with time to first AECOPD as the primary outcome and exacerbation rate as the secondary outcome. In this largely white (85%) cohort of North American patients with severe COPD (mean FEV $_1$ 1.12 L; 40% of predicted), the mean (SD) 25(OH)D $_3$ was 25.7 (12.8) ng/mL. A total of 33.1% of participants were vitamin D insufficient (≥ 20 ng/mL - <30 ng/mL); 32% were vitamin D-deficient (<20 ng/mL), and 8.4% had severe vitamin D deficiency (<10 ng/mL). Baseline 25(OH)D $_3$ levels had no relationship to time to first AECOPD or AECOPD rates, and the authors concluded that in patients with severe COPD, baseline 25(OH)D $_3$ levels are not predictive of subsequent AECOPD.^[22] In another study following 97 COPD patients at the Royal Free Hospital (UK), low 25(OH)D $_3$ levels were not associated with frequent exacerbations and did not increase susceptibility to human rhinovirus infection.^[23] In a randomised, single-centre, double-blind, placebo-controlled trial in Belgium, 182 patients with moderate to very severe COPD and a history of recent exacerbations were given 100 000 IU of vitamin D supplementation or a placebo every 4 weeks for 1 year. The primary outcome was time to first exacerbation. Secondary outcomes were exacerbation rate, time to first hospitalisation, time to second exacerbation, FEV $_1$, quality of life, and death. Mean serum 25(OH)D $_3$ levels increased significantly in the vitamin D group compared

with the placebo group. The median time to first exacerbation did not significantly differ between the groups, nor did exacerbation rates, FEV1, hospitalisation, quality of life, and death. However, a post hoc analysis in 30 participants with severe vitamin D deficiency (serum 25(OH)D₃ levels <10 ng/mL) at baseline showed a significant reduction in exacerbations in the vitamin D-deficient group.^[24] ViDiCO (Vitamin D Supplementation in Patients with Chronic Obstructive Pulmonary Disease), another recent study on vitamin D₃ supplementation in patients with COPD, found that supplementation protected against moderate or severe exacerbations, but not URTIs, in patients with baseline 25(OH)D₃ levels of >50 nmol/L.^[25] Vitamin D supplementation has also been suggested for improving physical performance, but a recent randomised trial did not show any benefits in this regard.^[26] Although vitamin D deficiency may contribute to morbidity in COPD patients, a lack of vitamin D does not appear to contribute to excess mortality.^[27]

Tuberculosis and vitamin D

The innate immune response is important in the defence against *M. tuberculosis*. Toll-like receptor triggering via vitamin D and cathelicidin is important in this response and may explain why black Americans, who are often vitamin D deficient, are more prone to contracting TB than are whites, and tend to have a more aggressive form of the disease.^[28] Vitamin D deficiency has been linked to a higher prevalence of TB, and this may in part be explained by genetic polymorphisms of the VDR and seasonal variation in vitamin D levels, which have also been linked to susceptibility to TB.^[29-33] The use of vitamin D as an adjunct to chemotherapy for TB has been tested in several clinical studies. Most of these studies have found beneficial effects, and a recent clinical trial in Pakistan, the SUCCINT (Supplementary Cholecalciferol in Recovery from Tuberculosis) study, showed accelerated clinical and radiographical improvement in those given supplemental high-dose vitamin D.^[34] They also showed an improved immunological response, which was borne out by Coussens *et al.*^[35] in another study.

Vitamin D, pneumonia and URTIs

Vitamin D regulates the production of the antimicrobial peptides cathelicidin and β -defensin-2 (β D2), which play an important role in the innate immune response to infection. Therefore, vitamin D may have a role in prevention and treatment of acute infections such as pneumonia.^[36,37] Vitamin D deficiency in children has been strongly associated with the risk of acute lower respiratory tract infections (LRTIs) in a number of settings. In Ethiopia, for example, researchers found that 42% of children hospitalised for pneumonia had rickets, or severe vitamin D deficiency.^[38] Associations between mortality and serum levels of 25(OH)D₃, cathelicidin and β D2 were investigated in a prospective cohort of 112 patients admitted with community-acquired pneumonia during winter in New Zealand. Severe 25(OH)D₃ deficiency (<30 nmol/L) was common in this population (15%), and was associated with a higher 30-day mortality rate compared with patients with sufficient 25(OH)D₃. These associations were not explained by differences in age, comorbidities or the severity of the acute illness. Neither cathelicidin nor β D2 levels predicted mortality, although there was a trend towards increased mortality with lower cathelicidin ($p=0.053$).

Neither cathelicidin nor β D2 levels correlated with 25(OH)D₃. The authors concluded that 25(OH)D₃ deficiency is associated with increased mortality in patients admitted to hospital with community-acquired pneumonia during winter.^[39] In a prospective cohort study of 272 hospitalised community acquired pneumonia patients, 25(OH)D₃, leukocytes, C-reactive protein, total cortisol, the Pneumonia Severity Index score and CURB-65 score were measured on admission. Major outcome measures were intensive care unit (ICU) admission and 30-day mortality. A total of 143 (53%) patients were vitamin D deficient (<50 nmol/L), 79 (29%) patients were vitamin D insufficient (50 - 75 nmol/L), and 50 (18%) patients were vitamin D sufficient (>75 nmol/L). Vitamin D deficiency was associated with an increased risk of ICU admission and 30-day mortality independent of other factors.^[40] There have been very few nutritional interventions aimed at the treatment or prevention of acute LRTIs published thus far. A randomised control trial in an area of high vitamin D deficiency in Afghanistan showed that one high dose of vitamin D₃ combined with antibiotic treatment reduced the reoccurrence of pneumonia in children aged 1 - 36 months who had been hospitalised for pneumonia.^[41] However, there are conflicting results from another randomised, placebo-controlled trial by the same group in the same area. Oral vitamin D₃ (100 000 IU, $n=1$ 524) was compared with a placebo ($n=1$ 522) and given to children aged 1 - 11 months in Kabul, Afghanistan. There was no significant difference between the incidence of first or only pneumonia between the vitamin D and the placebo group. The authors concluded that quarterly bolus doses of oral vitamin D₃ supplementation to infants were not an effective intervention to reduce the incidence of pneumonia in infants in this setting.^[42] In a study published by Choudhary and Gupta,^[43] short-term supplementation with oral vitamin D (1 000 - 2 000 IU per day for 5 days) had no beneficial effect on the resolution of severe pneumonia in under-5 children.

Vitamin D also modulates the innate response to respiratory viral infections.^[44] Monthly high-dose vitamin D₃ supplementation in elderly patients has been shown to reduce the incidence of acute respiratory tract infections.^[45] In immunosuppressed patients and those with frequent respiratory tract infections, vitamin D supplementation has been shown to be of benefit.^[46] In a recent meta-analysis of 25 randomised controlled trials, vitamin D supplementation was found to be a safe intervention, and it reduced the rate of acute respiratory tract infections, particularly in those who were initially vitamin D deficient. Those who were given daily or weekly doses benefited, but not those given bolus doses.^[47]

Vitamin D and cystic fibrosis

Vitamin D deficiency is common in young children with cystic fibrosis, even in children with pancreatic sufficiency.^[48] Higher levels of 25(OH)D₃ are associated with lower rates of pulmonary exacerbations and, in adolescents, with better lung functions, as reflected by a higher FEV1.^[49] Supplementation with vitamin D in patients with cystic fibrosis is a challenge because of poor absorption rates for vitamin D in these patients. In a recent pilot trial of vitamin D supplementation, higher doses of oral vitamin D were required to achieve adequate serum levels. The trial showed benefits of supplementation on quality of life, reduced inflammation and improved lung functions.^[50]

Conclusion

Vitamin D deficiency is associated with a number of respiratory diseases, with notable effects on respiratory infections and lung function. Supplementation with vitamin D appears to improve many lung conditions. The evidence for vitamin D supplementation is not so clear-cut in obstructive airways disease such as COPD and asthma, but it is definitely beneficial in TB, and new evidence is mounting that it may be useful in patients with acute respiratory tract infections, particularly in individuals that are vitamin D deficient. Trials in patients with cystic fibrosis are at an early stage. The optimum route and dose for vitamin D supplementation still needs to be worked out, but recent analysis favours daily or weekly supplementation over bolus dosing. The genetic variability of the VDR may impact on outcomes. The development of new vitamin D analogues that target the inflammatory pathway without affecting calcium metabolism will be something for the future.^[51]

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