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Perspective

Reconsidering Vitamin D Supplementation in Pulmonary Disease: The Case for Targeted Respiratory Delivery

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Abstract

Despite compelling epidemiological evidence linking vitamin D deficiency to adverse outcomes in chronic obstructive pulmonary disease (COPD), asthma, and cystic fibrosis, randomized controlled trials have consistently failed to demonstrate clinically meaningful benefits from oral vitamin D supplementation. This disconnect between observational associations and interventional evidence represents a significant paradox in pulmonary medicine. Recent meta-analyses have found limited protective or therapeutic effects of oral supplementation on exacerbation rates, lung function, hospitalizations, or quality-of-life measures. We propose that this therapeutic failure reflects not a lack of vitamin D's efficacy but rather a fundamental limitation in the route of delivery.

Oral vitamin D supplementation undergoes hepatic metabolism and systemic dilution before reaching respiratory tissues. High expression of cytochrome P450 family 24 subfamily A member 1, the vitamin D-inactivating enzyme, in pulmonary vasculature suggests that orally delivered vitamin D may be degraded before reaching the lung lumen. The respiratory epithelium possesses complete machinery for vitamin D activation, and vitamin D receptors are expressed throughout airway epithelial and immune cells, making direct pulmonary delivery mechanistically feasible. Preclinical studies demonstrate that nebulized or inhaled vitamin D reduces inflammation, protects epithelial barrier function, and improves lung function in murine models of respiratory disease without producing off-target systemic effects or hypercalcemia.

Direct lung delivery of vitamin D represents an unexplored therapeutic strategy that could transform management of chronic respiratory diseases, like COPD, by achieving local therapeutic concentrations while minimizing systemic exposure. Clinical trials investigating safety, dosing optimization, and efficacy are warranted.

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Abbreviations:

COPD=chronic obstructive pulmonary disease; **CYP2R1**=cytochrome P450 family 2 subfamily R member 1; **CYP24A1**=cytochrome P450 family 24 subfamily A member 1; **CYP27A1**=cytochrome P450 family 27 subfamily A member 1; **CYP27B1**=cytochrome P450 family 27 subfamily B member 1; **HP**=hypersensitivity pneumonitis

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Introduction

Since the incidence of asthma and allergy began rising in the late 1900s, much research has focused on understanding the causes behind this phenomenon. Initial evidence from epidemiological studies found increased asthma prevalence in developed countries, leading to the idea that increased time indoors led to decreased sunlight-driven vitamin D synthesis and lower vitamin D levels.[1] Since this initial idea, numerous studies have been conducted on the relationship between vitamin D and asthma, now expanding to other respiratory diseases, like chronic obstructive pulmonary disease (COPD), infections, and environmental exposures. However, despite compelling epidemiological evidence linking low vitamin D levels to increased exacerbations and reduced lung function in COPD, asthma, cystic fibrosis, and other respiratory pathologies, randomized controlled trials have consistently failed to demonstrate clinically meaningful benefits from oral vitamin D supplementation. Meta-analyses across lung diseases reveal a disconnect between observational associations and interventional evidence, with minimal effects predominating across study designs, dosing regimens, and sample sizes.

The Vitamin D Paradox

The failure of vitamin D supplementation to improve clinical outcomes represents one of the most significant examples of the "vitamin D paradox" in respiratory medicine, where strong epidemiological associations fail to translate into therapeutic benefits. Across trials, oral vitamin D supplementation has shown no consistent effects on lung function, exacerbation rates, hospitalizations, or quality-of-life measures in respiratory disease patients.[2-6] Observational studies across conditions consistently demonstrate strong associations between vitamin D deficiency and adverse outcomes.[7] Patients with COPD with vitamin D deficiency show higher hospitalization rates and more frequent exacerbations. In asthma, low vitamin D levels correlate with increased exacerbation rates, reduced lung function, and poor symptom control.[8] Cystic fibrosis patients, who experience near-universal vitamin D deficiency due to malabsorption, exhibit associations between low vitamin D and worse respiratory outcomes. However, in supplementation studies, the results were overwhelmingly negative.[9] A 2024 Cochrane review for COPD found little to no changes in exacerbation rates, lung capacity, or quality of life with supplementation.[10] Similarly, a 2023 updated Cochrane review for asthma reversed the conclusions of their 2016 review, finding no protective effects against exacerbations.[8]

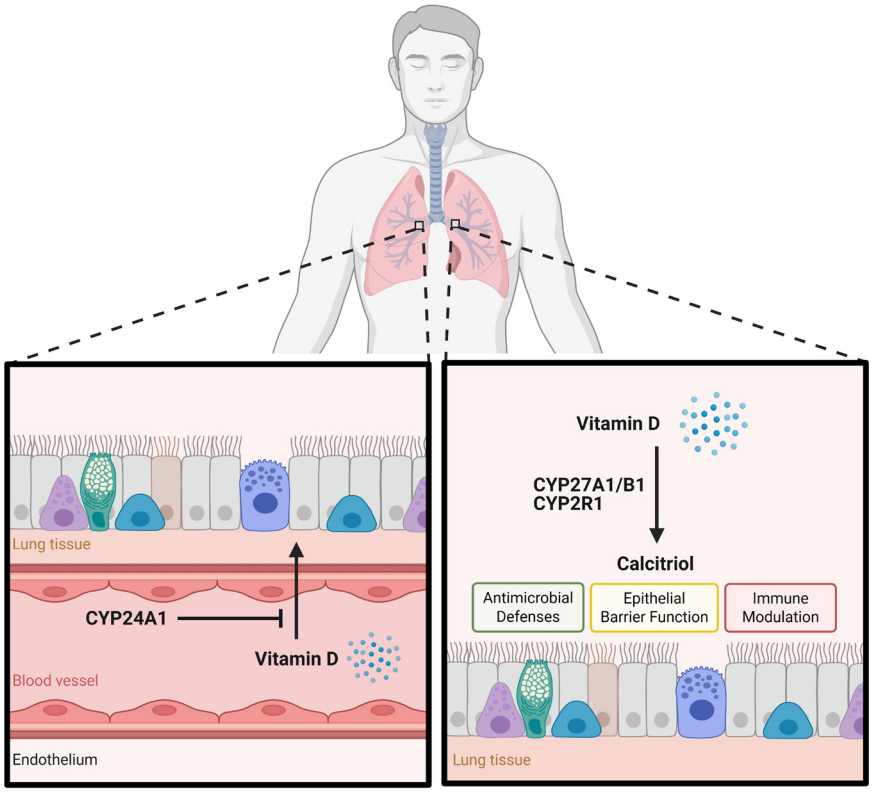
The evolution of lung disease trial evidence illustrates the broader pattern of oral vitamin D supplementation failures. Early promise from smaller studies gave way to negative results from large, well-designed trials. Cystic fibrosis presents the most compelling case for vitamin D supplementation, with 90% of patients experiencing vitamin D deficiency due to malabsorption.[5] Yet clinical trials consistently demonstrate that correcting circulating levels of vitamin D deficiency fails to produce clinical benefits. Across all 3 diseases, oral vitamin D supplementation failed to improve the most clinically relevant outcomes. Lung function measures, including forced expiratory volume in 1 second and forced vital capacity, showed no consistent improvements, exacerbation rates remained unchanged, and hospitalization rates and quality-of-life scores were similarly unaffected. Even in severely deficient populations, benefits are modest and inconsistent. Meta-analyses of COPD and asthma trials found protective effects primarily in patients with baseline levels <25nmol/L, but this represented a small subset of study participants.[2,6]

Oral Supplementation Versus Direct Delivery to the Airway Epithelium

Despite extensive documentation of vitamin D deficiency in pulmonary disease populations and compelling mechanistic evidence from in vitro and in vivo studies, systematic reviews and meta-analyses have consistently failed to demonstrate meaningful clinical benefits from oral vitamin D supplementation across respiratory conditions. The numerous clinical disappointments necessitate critical re-examination. We posit that the fundamental limitation lies not in vitamin D's therapeutic potential but in our approach to its delivery. Oral vitamin D supplementation is subject to hepatic metabolism, systemic dilution, and most notably, potential inactivation before reaching target tissue in the respiratory tract. A recent study of vitamin D-related genes in human lung tissue found that cytochrome P450 family 24 subfamily A member 1 (CYP24A1), the enzyme responsible for inactivating the biologically active form of vitamin D to the form that is eventually excreted, was highly expressed in pulmonary vascular endothelial cells.[11] This suggests that oral vitamin D may be inactivated before reaching the lung lumen and thus, ineffective in exerting therapeutic effects in the lungs at clinically relevant levels.

Therefore, direct delivery of vitamin D to the airway epithelium through topical or inhaled administration may provide a more effective route for treating lung disease. The respiratory epithelium possesses complete machinery for vitamin D metabolism, including expression of cytochrome P450 family 27 subfamily B member 1 (CYP27B1) for local calcitriol synthesis and expression of vitamin D receptors across airway epithelial and immune cells (Figure 1).[12] The biologically active form of vitamin D, calcitriol, exerts pleiotropic effects within the airways, including upregulation of antimicrobial peptides such as cathelicidin and β-defensins, enhancement of epithelial

Figure 1. Vitamin D Oral Supplementation Versus Inhaled Delivery



CYP24A1=cytochrome P450 family 24 subfamily A member 1; CYP27A1=cytochrome P450 family 27 subfamily A member 1; CYP27B1=cytochrome P450 family 27 subfamily B member 1; CYP2R1=cytochrome P450 family 2 subfamily R member 1

barrier function through tight junction proteins, modulation of inflammatory cascades via nuclear factor-κB and mitogen-activated protein kinase pathways, and augmentation of antioxidant defenses. Vitamin D's capacity to bolster these defenses while simultaneously modulating inflammatory responses positions it as an ideal therapeutic candidate for respiratory conditions characterized by oxidative stress and inflammation.

Several recent preclinical studies have explored this approach in vivo, producing promising results. Serré et al demonstrated that nebulized vitamin D reduced inflammatory cell infiltration and protected epithelial barrier function in lipopolysaccharide-exposed mice, without altering systemic vitamin D levels.[13] This proof-of-concept study highlights the potential for achieving local therapeutic effects while minimizing systemic exposure. Another group has also published several studies investigating inhaled vitamin D as a method to restore local vitamin D levels and to treat hypersensitivity pneumonitis (HP) and pulmonary fibrosis in murine models, finding beneficial effects against HP-induced collagen deposition, epithelial-mesenchymal transition, and lung function decrements.[14-16] Vitamin D dry powder formulations have also been explored as an adjunct therapeutic for tuberculosis.[17,18] Additionally, pulmonary administration of vitamin D treatment in murine models of COPD induced alveolar regeneration and improved lung function.[19,20] Nasal delivery of vitamin D has also shown promise in models of sinonasal disease and infection.[21-24] In vitro studies using primary airway cells at air-liquid interface have shown that apical application of vitamin D enhances antimicrobial peptide expression, reduces pathogen-induced inflammation, and can protect against pollutant-induced oxidative stress, suggesting direct epithelial effects independent of systemic metabolism.[25,26] The potential benefits of inhaled vitamin D extend across the spectrum of chronic respiratory diseases, being able to combat chronic inflammation and oxidative stress as well as bolstering antimicrobial defenses. Additionally, the in vivo studies discussed seem to show no evidence of adverse effects such as hypercalcemia, and in several studies, did not lead to significant changes in circulating vitamin D levels.[27,28] Key limitations to the existing studies are the focus on ex vivo and animal studies, with most encompassing short exposure periods.

Conclusions

To the best of our knowledge, no clinical trials have investigated pulmonary delivery of vitamin D in individuals with chronic lung diseases, like COPD, despite promising preclinical results. As such, future work should establish human safety data (especially in the context of

prolonged exposure), dosing and delivery optimization, pharmacokinetics/pharmacodynamics, and clinical utility. A challenge of pulmonary drug delivery is that most agents are fat soluble (and thus, poorly water soluble) limiting drug dosage. Given that vitamin D is fat-soluble, further preclinical work is needed on formulation and in vivo effects in relevant animal models.[29] Additionally, more extensive work on the pharmacokinetics of oral vitamin D, especially in the pulmonary compartment, may help elucidate why correction of circulating vitamin D levels does not lead to clinical benefits. To date, work on pulmonary delivery has largely focused on in vitro and animal studies, therefore, we hope this piece leads to further research and discussion on this topic and eventual translation to clinical utility.

The disconnect between vitamin D's mechanistic promise and clinical disappointment in respiratory disease reflects a fundamental mismatch between therapeutic target and delivery method. By reconceptualizing vitamin D as a local respiratory therapeutic rather than a systemic supplement, we can potentially unlock its therapeutic benefits. As we continue to face challenges from air pollution, emerging respiratory pathogens, and the growing burden of chronic lung disease, evaluating vitamin D through the lens of pulmonary delivery could offer a targeted approach to enhance pulmonary defense mechanisms. This delivery strategy may also benefit other vitamins and nutraceuticals implicated in lung disease such as omega-3 fatty acids and vitamin E.[30-35] Direct pulmonary delivery of vitamins and nutrients presents an under-explored and promising approach for treating lung disease and warrants further investigation.

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Declaration of Interest

The authors report no conflicts of interest related to this work.

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