Impact and Influence of Deficiency of Vitamin D on Asthma in School-Aged Children

Zainab S Abdul_hafed Shagloof [1*],Najia Albashir Mahdawi[2]

[1*] Pediatric department, Primary Health Care Corporation, Doha. Qatar

[2] Medicine Department, Faculty of Medicine, Gharyian University, Libya

*zainabshaglouf@gmail.com , Najia.mahdawi@gu.edu.ly

ABSTRACT

Over the past few decades, environmental modifications (lower availability to sunlight owing to operating indoors or use of protective clothing and sunblock; food modifications) have been mainly blamed for vitamin D and inadequacy in the wider public. Being overweight, living in the inner-city and having African American ancestry are possible causes for asthma and vitamin D insufficiency. While the musculoskeletal effects of chronic insufficiency of vitamin D are very well recognized, a variety of other illnesses, particularly respiratory problems, have recently been related to vitamin D insufficiency. The potential significance of vitamin D as an increasing mediator that supports lung health is becoming well understood. In children with asthma, vitamin D insufficiency appears to be more common. According to epidemiological data, children with asthma with low blood levels of vitamin D suffer from more pain, exacerbations, lung damage, medication usage, and severe illness. Research published in vitro has shown that adult asthmatics' steroid sensitivity is improved by vitamin D. By preventing disease, in particular by retaining regulatory T cells, and by directly inducing intrinsic antimicrobial systems, vitamin D may have a significant impact on lung health. To resolve the diagnosis and treatment significance vitamin D could have in treating asthma in the long term, more investigations are essential to completely comprehend the impacts of vitamin D in preserving airway homeostasis. Along with prospective defence mechanisms like antiviral impacts and augmented steroid attentiveness, considerable uncertainty concerning the impacts of vitamin D insufficiency and inadequacies in kids with asthma and a thorough analysis of present experimental and observational studies substantiation of relationship among vitamin D levels and asthma or bronchitis comorbidities.

Keywords: children, asthma, vitamin d, deficiency.

Introduction

One of the most prevalent inflammatory response disorders in children, asthma is often the first in 50% of instances; indications are first seen in childhood. Asthma is a serious public health issue in the United States and worldwide. Uncertain factors led to a rise in the incidence of chronic diseases from before the 1960s until about the 1990s. The origins of the "asthma pandemic" are not realized, despite new data that shows minimal or slight additional growth in asthma rates in nations with high illness prevalence. Asthma prevalence and costs have been rising in both industrialized and developing countries. Due to hospitalizations, emergency department visits, and academic absences, asthmatic is among the most serious pediatric illnesses. An important nutrient with a unique molecular mechanism is vitamin D. Asthma prevalence has been rising along with an increase in vitamin D insufficiency [1]. The ultraviolet (U.V.) element of sunlight determines how much natural vitamin D source is produced by dermatological synthesis (around 80%). The rising incidence of vitamin D insufficiency is assumed to be related to acquiring a Western-style lifestyle, changing food habits, and reduced time spent engaging in recreational recreation. By enhancing immunological functioning, displaying anti-inflammatory actions, decreasing steroid sensitivity, boosting the effects of glucocorticoids, shortening cellular proliferation, and lowering remodelling, vitamin D has been hypothesized to contribute to the pathophysiology of asthma. Numerous types of research have shown a link between asthmatic and vitamin D insufficiency, although the data is still inconclusive. According to several cross-sectional investigations, children with asthma had lower blood vitamin D levels than children without asthma. A few studies have suggested that elevated blood vitamin D concentrations might lead to greater asthma comorbidities, although other investigations have not found such a strong correlation. According to research on asthmatic patients, there may also be a relationship between vitamin D levels and asthma intensity, recurrence, emergency departments, and length of hospitalization [2].

UVB radiation on the skin and food intake are the two main sources of vitamin D. Cod liver oil, seafood, liver, egg whites, and nutraceuticals are examples of dietary components. Exposure to light is the main predictor of vitamin D levels in people because very few foods contain it. It is predicted that 20 to 30 mins of midday solar radiation on the face and forearm in fair-skinned individuals will produce the equivalents of around 2000 I.U. of vitamin D. In the warmer months in the U.K., two or three of these types of sun excursions per week are

enough to attain appropriate vitamin D levels.8 In the presence of enough sunlight exposure, at least 850-1500 IU (20–25 mg) of vit D may be required daily [3,4]

Impacts of Vitamin D on the Physiology

Sunlight is the main source of vitamin D in humans. Solar UVB radiation photolyzes 7-dehydrocholesterol in the skin to create vitamin D3, which is then converted into vitamin D3, also called Cholecalciferol. The liver transforms Cholecalciferol from food and the skin into 25-hydroxyvitamin D3 (25[O.H.]D), which is then stored. The parathyroid hormone maintains calcium-phosphate balance by regulating the hydrogenation of 25(O.H.)D to its biologically activated state,25[O.H.]2D3 in the kidneys. To regulate gene expression, 1,25(O.H.)2D3 must first attach to the vitamin D receptor (VDR), forming a heterodimer with both the retinoid X receptor. This heterodimer must bind to genomic regions known as vitamin D-specific receptors (VDREs) [5].

The metabolic pathway of 25(O.H.)D in extrarenal sites and the varying gene expression linked to cancer and antibody activation in response to vitamin level suggest that vitamin D may have various effects on humans. To ascertain if vitamin D levels are appropriate, measurements of serum or plasma concentrations of 25(O.H.)D, the primary systemic form of vitamin D linked to secondary hyperparathyroidism and skeletal diseases, including rickets, are taken [6].

Serum 25[O.H.]D is the best indicator of one's total vitamin D levels since it includes total vitamin D through nutrition and sun doses, as well as the liver's production of Vit D from adipose stores. There are no accepted recommendations on the best serum 25[O.H.]D concentrations. Most specialists agree that a 25[O.H.]D level of less than 50 nmol/L constitutes vitamin D insufficiency (20 ng per millilitre). Until the earlier reaches 75 to 100 nmol/L (30-40 ng per millilitre), parathyroid hormone levels are negatively associated with 25[O.H.]D levels before parathyroid hormonal changes start to level off. When 25[O.H.]D concentrations increase from an average of 50 to 80 nmol/L, intestinal calcium transport rises by 45 to 65%. (20 to 32 ng per milliliter). Based on the information mentioned above and its correlation with health outcomes, 25[O.H.]D values between 50 and 75 nmol/L (20 to 30 ng per millilitre) are regarded as diagnostic of vitamin D deficiency. Normal vitamin D levels range from 75 nmol/L (30 ng per milliliter) to 100 nmol/L for 25[OH]D. It is uncommon to

become too intoxicated on vitamin D. When 25[O.H.]D concentrations increase from an average of 50 to 80 nmol/L; intestinal calcium transport rises by 45 to 65%. (20 to 32 ng per milliliter). Based on the information above and its correlation with health outcomes, 25[O.H.]D values between 50 and 75 nmol/L (20 to 30 ng per millilitre) are considered diagnostic for vitamin D deficiency. Normal vitamin D levels range from 75 nmol/L (30 ng per milliliter) to 100 nmol/L for 25[OH]D. It is uncommon to become too intoxicated with vitamin D [7].

Vitamin D Deficiency

Skin hyperpigmentation levels, age, factors are influencing sun damage (latitude, seasons, time spent outside, and clothes), fat percentage, and sunblock use all impact vitamin D skin synthesis. Supplements and dietary consumption, which primarily comes from fatty fish, fortified cereals, and milk products, are secondary sources of vitamin D. Due to the enormous influence on the therapeutic evaluation of vitamin D insufficiency, this recently suggested criterion of vitamin D sufficiency (i.e., >20 ng/ml) has caused much debate. As a result, opinions on the ideal vitamin D levels for non-musculoskeletal health are divided. Irrespective of the cutoff point, vitamin D deficiency or inadequacy has probably become more prevalent in the U.S. due to dietary and behavioural responses (such as reducing time spent outside) [8].

Immune System

The impacts of Vit D on the immune system's innate and adaptive systems have been reported to be significant yet incompletely understood. Vitamin D's ability to modulate the immune response is supported by the presence of VDRs and the hydrogenation of 25(O.H.)D in relevant cellular processes, including both dendritic cells and macrophages. In scientific investigations, vitamin D has been shown to impede the propagation of CD41 T cells and to decrease the emission of Th1 cytokines and IL-17. Studies on Th2 cytokines and vitamin D have shown mixed findings. For instance, vitamin D has indeed been demonstrated to boost and decrease IL-4 generation by cultured naïve T cells. Vitamin D or UVB light has been demonstrated to suppress allergic inflammation of the airways (AAI) in mouse models and lower IL-4 concentrations in bronchoalveolar lavage. VDR knock-out animals exhibit higher serum concentrations of IL-13 and IgE but do not produce asthmatic inflammatory responses, confirming a crucial function for VDR lung transcription in airway inflammation. This is

congruent with the possibly complicated supplemental vitamin D on asthmatic. Asthma aetiology may be influenced by vitamin D in one method through regulating Regulatory t cells (Tregs). It's been suggested that vitamin D, combined with corticosteroids, helps naïve T cells differentiate into IL-10-secreting Tregs.

Additionally, it has been demonstrated that vitamin D works through IL-10- and TGF-b-dependent pathways to raise blood levels of the immune-suppressive cytokine TGF-b and IL-10 in people and to improve the outcomes of allergen immunotherapy in mice AAI. These pathways and the role of vitamin D related to respiratory factors are illustrated in Figure 1. Vitamin D inhibits dendritic cell Ox40L, which is necessary for Th2 activation and increases TGF-b in effector T cells. That causes a rise in TGF-b-positive Tregs and a decrease in Th2 cytokine production [9, 10].

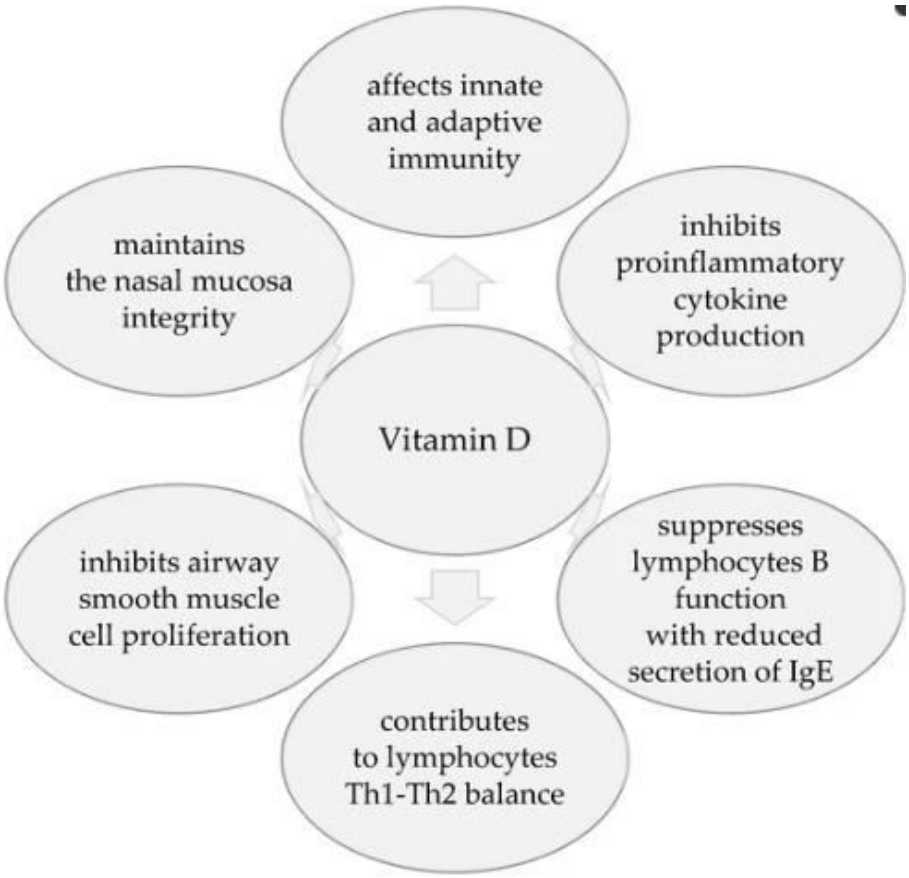

Figure 1. Schematic representation of the role of vitamin D in various respiration-related factors reproduced with permission from [9].

According to a cross-sectional investigation of Finnish people, the supplementation of Vitamin D, tested in infant kids, is related to higher asthma risk. Nevertheless, this trial excluded vitamin D measurements and had insufficient individual follow-up information. Contradictory findings emerged from particular instance research investigating the

correlation between asthmatic and blood vitamin D in interracial kids and adolescents as well as British adults inadequacy of information on vitamin D levels in infancy and potential bias in screening were limitations of both trials. Birth cohort studies allow us to proactively evaluate the relationship between an environment and the desired result. Even though a prospective study of children from Britain found a significant correlation between late-pregnancy blood vitamin D levels and asthma at age 9, there was insufficient follow-up with the enrolling kids. Birth observational studies in Chicago, Ireland, Tokyo, and Sweden (each with >750 mother-child pairings) have demonstrated a negative relationship between maternal dietary consumption of vitamin D throughout childhood and childbirth, childhood wheezing and recurring wheezing or asthma. All investigations were constrained by very short follow-up periods (ranging from 1.3 to 5 years, making it difficult to diagnose asthma), considerable loss to adopt, and a lack of measurements of blood vitamin D levels during gestation or childhood. Another prospective birth study of kids in New Zealand discovered an inverse relationship between the levels of vitamin D in cord blood and gasping by the time they were five years old, but not with incident asthma. However, a prospective birth study on children from New Zealand indicated a link between vitamin D levels at 5 years old and asthma in males at 15 years old, the results were uncorrected for confounding variables, and the research lacked vitamin D measurements in formative years. In conclusion, there is inadequate proof that vitamin D levels and asthmatic are causally related. The negative relationship between maternal vitamin D consumption during gestation or vitamin D levels in blood products and childhood wheezing was discovered in further ongoing studies [11].

Vitamin D and Asthma Morbidity

Determining how vitamin D guards against someone or lowers asthma morbidity is of great interest, in addition to its possible function in basic asthma prevention. The results of the cross-sectional investigation do not support a temporal or causal relationship between Vit D and asthmatic severity. In a study, a thorough analysis of blood vitamin D levels in approximately 1000 children from America with moderate to severe chronic asthma who had experienced at least one hospitalization or a trip to the emergency room, a 25[O.H.]D level of 30 nanograms/ml at baseline were linked to an elevated risk of serious asthma over the subsequent 4 years. The size of the reported connection was stronger in kids with vitamin D deficiency that did not get inhaled steroids (ICS) than those with appropriate levels of vitamin D or those who did not obtain ICS but did. This discovery, with others (listed below), points to the idea of vitamin D improves steroid response. However, it appears that significantly

fewer children in the vitamin D group (n = 14.4, or 17%) experienced asthma exacerbations than in the versus placebo (n = 14.11, or 46%). Children in the treatment group were less likely to experience a drop in vitamin D concentration throughout the experiment. Results from this tiny medical trial should be read cautiously since asthma exacerbations were not assessed according to a conventional method, and there was no appreciable change in pulmonary function or discomfort score [12]. Levels Of vitamin d in Italian asthmatic children are favourably connected to asthma management and negatively linked with strength training bronchoconstriction, according to 2 minor cross-sectional investigations. Perplexing and inverse causality cannot be ruled out as possible reasons for these results, though. Epidemiological studies and a short clinical study have provided intriguing and conclusive evidence suggesting vitamin D may be protective against asthma flare-ups [13].

Performance management of cathelicidin and CD14 increased distinctions, and recruiting and selecting macrophages increased output of 25(O.H.)D to its activated state (1,25(O.H.)2D3), and potentiation of host defences against Mycobacteria and other microbes, microorganisms, and pathogens are just a few of the antibacterial properties of enterocytes. Influenza outbreaks and vitamin D insufficiency have seasonal patterns in common. Research on kids and parents has shown a negative correlation between vitamin D status and the incidence of chest diseases. Reduction in blood vitamin D was linked to a higher risk of identity upper respiratory tract infections, especially in patients with pulmonary disease or asthma, according to a U.S. cross-sectional research of over 19,000 individuals 12 or older. Two medical studies on the use of vitamin D to avoid or alleviate the symptoms of adolescent respiratory tract infections either had no results or negligible results. Limited follow-up periods, low vitamin D dosages, and non-microbiological assessments of lung problems are some of the studies' shortcomings. According to a study, supplementing with vitamin D3 (1,200 IU/day) over the colder months helped 167 people experience less influenza A. Still, not influenza B. Supplements decreased the likelihood of illness asthma attacks in asthmatic children, according to a subgroup study. A comprehensive observational research of 280 Finnish children hospitalized with a wheezing disease found that vitamin D level was negatively proportionate to co-infections with adenovirus or rhinovirus, providing more evidence for vitamin D's preventative capabilities.

A recent study demonstrated that adding vitamin D to cell cultures boosts the steroid production of IL-10 by Tregs, with consequences ex vivo in individuals with comparable

microtubule asthma. Cross-sectional experiments of kids and adults had also demonstrated that low vitamin D levels are linked to poor pulmonary function, enhanced performance-enhancing drugs use, or lowered in vitro steroid response (although by what appears to be an IL-10-independent mechanism). This is indicative of the fact that vitamin D plays a part in improving steroid sensitivity. Results were obtained on the down-regulation of atopy point to complicated and inexplicable supplemental vitamin D on host defence. These contradictory results are similar to those reported for specific allergens or allergic rhinitis. There are inadequate or poor supporting data for a relationship between vitamin D level and atopy or atopic illnesses apart from asthmatic. The incapability to rule out perplexing or collection bias (due to disparity loss of follow-up) as potential explanations for the results obtained, as well as the absence of an appropriate evaluation of vitamin D status or allergic responses, limits the understanding of the existing research of vitamin D and atopy [14].

Therefore, it's probable that early-life vitamin D shortage or insufficiency generally leads people to gasp in preschool. Low serum 25(O.H.)D levels in the umbilical cord were linked to an elevated prevalence of childhood wheezing in a New Zealand population of children. Children born to inner-city moms who were vitamin D-deficient throughout their mothers are more likely to have recurring wheezing when they are 3 years old. Childhood development wheeze and vitamin - D consumption throughout gestation is negatively correlated. Children of mothers with lesser vitamin D consumption had a higher risk of subsequent wheezing at age 5 years, according to a natal cohort study in Scotland. Spirometry or the amount of breathed nitric oxide was not associated, though. In a mother-child epidemic outbreak, higher maternal vitamin D consumption in the first and third semesters was linked to a decreased incidence of asthmatic and wheezing in children. According to a different study, there is a negative correlation between maternal vitamin D consumption throughout gestation and the onset of allergies and asthma in 5-year-old offspring. Many of these investigations were constrained by dietary assessment methods rather than blood vitamin D status. Compared to age-matched samples, kids with a wheezy sickness classification had a much more than 2.5 times high prevalence of rickets. When serious rickets was prevalent, the risk of wheezy illness increased by 10-fold. Increased dynamic airway collapsing is made possible by chest wall relaxation. In conclusion, vitamin D shortage and inadequacy throughout pregnancy and the early years of life are linked to a higher risk of wheezing. Nevertheless, correlation does

not imply causality, and more research is required to determine vitamin D's precise function in wheeze aetiology [15].

Obesity and vitamin D levels have a complicated and reciprocal relationship. Because more vit D is stored in adipose in obese people, there is a contrary relationship between blood vitamin D concentrations and total body fat. Conversely, vitamin D may affect adipogenesis and lipofibroblast development in the uterus. Conditions linked to low vitamin D levels in gestating women (fat) and subsequent newborns (delivery in the winter) have already been linked to higher birth weight and future childhood obesity. A higher risk of acquiring more adiposity throughout a 2-year follow-up period was related to baseline vitamin D levels that were lower in Colombian students. Even becoming overweight and obese has been connected to asthmatic and increased disease severity in both kids and adults; the notion that supplementing with vitamin D reduces asthma morbidity by having good results in weight control is acceptable but very speculative. Per cross-sectional research of 14,000 American individuals, vitamin D shows a good correlation with pulmonary function measurements. In deficient mice, plethysmography and the forced oscillatory methodology were used to make comparisons of the lung capacity and features of the descendants of 2 categories of female BALB/c mice (one group was fed a vitamin D-sufficient diet, as well as the other group, was fed a vitamin D-insufficient diet) and b Vitamins male mice. In that scenario, it was demonstrated that mice born to vitamin D-deficient mothers had lowered lung function (mainly through lowered lung volume) despite alterations in cellular proliferation. It was possible that the anatomy of the alveoli had changed, although there was only research suggesting this. Such findings align with a previous study that found that pups of vitamin D-deficient rats had reduced lung responsiveness. It has been discovered that enhanced respiratory function in mice with VDR gene polymorphisms. In particular, vitamin D has been shown to encourage the production of DNA and surfactants in alveoli type II cells, and it could even regulate alveolarization.

Therefore, vitamin D deficiency may affect tumour growth in the uterus, enhancing asthma severity or predisposing individuals to developing asthma. Furthermore, vitamin D may affect asthma by controlling the transcriptional activity associated with the condition. Recent research has shown that the VDR binds to between 2,000 and 3,000 genes in lymphoblastoid and pre-osteoblastic cell lines. A portion of these genes—between 200 and 1,000—show

different expressions in response to calcitriol stimuli, and many of these genes are involved in autoimmune mechanisms [16].

Summary and Future Directions

Studies on animals and people reveal that vitamin D positively affects allergies and asthma morbidity. Nevertheless, until existing and upcoming medical testing is finished, a suggestion for or against treatment as a preventative or adjuvant drug for the treatment could be given due to the inherent limitations of the survey study. If the outcomes of these drug testing are encouraging, more research will be required to determine how best to provide and dose vitamin D supplements to cure or prevent allergies. If vit D does indeed help asthma, it is important to look into possible protective mechanisms. Most of the available research consistently supports vitamin D's positive effects on asthma. The reported negative relationships between vitamin D levels and severe asthma aggravation in children can be explained by severity by preventing infectious diseases and increased steroid responsiveness, alone or in combination. However, a key preventative effect of vitamin D towards asthma may eventually be explained by the down-regulation of Th2 immune function; there's scant and conflicting proof for a connection connecting vitamin D reactions. For instance, the reported negative link between vitamin D consumption or status throughout gestation and wheezing even before the age of five may be explained by antiviral characteristics.

Research is ongoing to determine whether or not vitamin D's ability to prevent asthma by encouraging healthy lung growth is true. Clinicians frequently inquire about the need to test asthma patients for vitamin D shortage or inadequacy. There is no proof in favour of such testing to manage asthma. However, it might have been prudent to check the vitamin D levels of both children and adults who belong to racial or ethnic minorities that seem to be especially prone to vitamin D deficiency, including races such as American people and individuals who are seriously obese or receive insufficient direct sunlight (such as people who are institutionalized). People should take vitamin And mineral supplements if their serum vitamin D (25[O.H.] D) concentrations are minimal than 20 ng/ml since their physical health may be in danger. Medical studies that are still being conducted should provide important insights into how vitamin D supplements might prevent the onset of pediatric asthma and lower asthma mortality. Prospective medical studies should investigate the following issues: If the nutrients reduce acute asthmatic worsening or improve medication compliance in school-aged kids (as an adjuvant to ICS); If vitamin D is more effective in

preventing iron deficiency in people from ethnic populations at risk; if vitamin D is more preventive towards viral infections; and if vitamin D prevents infant asthmatic when given in uterus (with or without intake during pregnancy)[17].

Conclusion

Vitamin D may affect asthma, which is now understood to have a complicated function in children's immune systems by regulating several immune-related processes. By decreasing inflammation, partly by retaining regulatory T cells, and directly inducing innate antimicrobial processes, vitamin D may be particularly vital for the body of the lungs and, more particularly, for the treatment of asthma. Current findings have shown links involving vitamin D and lung function, inflammatory indicators, and drug response regulation. Nevertheless, interventionist trials are necessary to demonstrate the theory that vitamin D deficiency promotes or exacerbates childhood wheezing, asthmatic, or medication tolerance.

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