The role of vitamin D in asthma and the effect of supplementation

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Abstract

Vitamin D deficiency is a global public health issue and has been associated with an increased incidence and severity of many diseases including diseases of the respiratory system. Due to westernized lifestyles, with spending more time indoors, there has been an increase in asthma and allergy as a result of vitamin D deficiency. Asthma is a chronic inflammatory disease of the lungs and the number one chronic disease in children. The vitamin D receptor (VDR) is expressed in cells involved in the immune/inflammation system in the human body, which provides the biological basis for the role of vitamin D in inflammatory diseases. In this thesis, the effect of vitamin D deficiency on asthma onset, pathophysiology and exacerbation will be discussed as well as the effect of therapy with vitamin D supplementation.

Gupta et al. measured serum 25(OH)D levels from children with moderate and steroid resistant asthma, and non-asthmatic children. They discovered that serum 25(OH)D levels were lowest in children with steroid resistant asthma. Damera et al. demonstrated that 1,25(OH)2D can inhibit ASM cell proliferation in both normal and asthmatic subjects by preventing cell cycle progression.

Birth cohort studies have shown that lower maternal dietary intake of vitamin D during pregnancy can be related to an increased risk of wheeze and development of asthma in children. Children from a mother with serum 25(OH)D concentrations of > 75 nmol/L had an increased risk of asthma at nine years of age, reported Gale et al.

Higher levels of vitamin D are associated with fewer asthma exacerbations in asthmatic children between 6 and 14 years old. An inverse correlation in asthmatic children between corticosteroid use and vitamin D levels was stated by Searing and colleagues. Studies have revealed that stimulation of ASM cells with VDR ligand, 1,25(OH)2D, control the expression of the genes coding for glucose-6-phosphate dehydrogenase and 1ß-hydroxysteroid dehydrogenase type 1 enzyme, which are both responsible for corticosteroid activation.

Vitamin D supplementation in infancy has been associated with increased atopy and allergic rhinitis in adulthood. Increasing 25(OH)D levels were associated with increasing risk of allergic rhinitis among adults in NHANES III. The conflicting data indicate the need to demonstrate the effect of vitamin D on the prevention and control of allergic diseases.

Much of the data support the hypothesis that higher vitamin D levels lead to better asthma outcomes. However, vitamin D deficiency is often an indirect marker of other confounding factors such as physical activity, making it hard to determine a causal association between vitamin D status and asthma.

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Introduction

Vitamin D deficiency has become an important public health issue.[1] Vitamin D is mainly known for its effects in calcium homeostasis and bone mineralization.[2] A change of behavior has caused people to spend more time indoors away from the sun, a decreased intake of vitamin D-containing foods, leading to vitamin D deficiency.[3] Recently, research has found that the sunshine vitamin (vitamin D) may play a role in several diseases involving the respiratory system. Epidemiologic data suggests an association between vitamin D deficiency and asthma.[4]

Asthma is a chronic inflammatory disease of the lungs and the number one chronic disease in children. [5] Symptoms of asthma are wheezing, coughing, chest tightness, and shortness of breath.[6] The inflammation of the airways makes it swollen and sensitive which causes the airways to react very strongly to certain inhaled (harmless) substances. The inflammation of the airways goes along with the pathological T helper cell type 2 (Th2) mediated immune response.[7] When this happens, the muscles around the airways tighten, narrowing the airways, causing less air to flow into the lungs. The swelling can also worsen, making the airways even narrower. Cells in the lungs might make more mucus than normal, which can further narrow the airways. This chain reaction can result in asthma symptoms. Therapy exists of an inhaled corticosteroid, to which additional controllers can be added if asthma control is incomplete. An inhaled beta 2 agonist (LABA), montelukast or theophylline can be added. Oral corticosteroids (prednisolone) can be added if there is still no asthma control.

Vitamin D has two physiologically relevant forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol).[8] Vitamin D3 is most effective in maintaining the level of circulating 25-hydroxyvitamin D3, a marker of vitamin D status.[9] Production from 7-dehydrocholesterol in the skin by ultraviolet B and dietary intake (oily fish, dairy products and supplements) are the main sources of vitamin D3.[10] In the liver, vitamin D3 is metabolized to 25-hydroxyvitamin D3 by vitamin D 25-hydroxylase.[11] This is further hydroxylated by the enzyme 25-hydroxyl vitamin D3-1α-hydroxylase (CYP27B1) to the active form: calcitriol (1,25-dihydroxycholecalciferol [1,25{OH}$_2$D$_3$]).[12] 1,25(OH)2D3 activates the vitamin D receptor (VDR), a nuclear receptor and ligand-activated transcription factor.[13] CYP27B1 and VDR are expressed in cells involved in the immune/inflammation system in the human body, which provides the biological basis for the role of vitamin D in inflammatory diseases.[14]

Recent discoveries have brought to light how other cells in different organs express vitamin D receptors. Examples are T and B lymfocytes, monocytes, antigen presenting cells (APC) including macrophages and dendritic cells.[15] This indicates the effects of vitamin D on the immune system, especially increasing the expressing of cathelicidins hCAP18.[16] HCP18 is an important defense factor against pathogens of the respiratory tract. Cathelicidins produced by neutrophils and epithelia, after a signal mediated by inflammatory cytokines, would seem to determine the chemotaxis of the cells of innate immunity by activating an inflammatory response against several microorganisms.[17] Moreover, vitamin D may stimulate the

production of cationic peptides, beta-defensin 2 and 4. One of the main effects (non-skeletal) of vitamin D is to modulate the immune response to pathogens.[18]

Vitamin D deficiency has been found to increase the risk of severe asthma exacerbation. The hypothesis which is adopted in this thesis is: *higher vitamin D levels lead to better asthma outcomes and vitamin D supplementation decreases asthma severity*. The effect of vitamin D deficiency on asthma onset, pathophysiology and exacerbation will be discussed as well as the effect of therapy with vitamin D supplementation.

Vitamin D and asthma

Due to westernized lifestyles, with spending more time indoors, there has been an increase in asthma and allergy as a result of vitamin D deficiency.[19] Sun exposure is important in asthma, because of the positive correlation between latitude and asthma prevalence.[20] The UV exposure decreases when you increase the distances away from the equator. These findings suggest that vitamin D may play a role in asthma pathogenesis.

The onset

Early in life, signs of disease, including airway remodeling, may be present.[21] Birth cohort studies did research for linkage between maternal vitamin D status and the beginning of asthma in children. These studies have shown that lower maternal dietary intake of vitamin D during pregnancy can be related to an increased risk of wheeze and development of asthma in children.[4][22][23]
Children from a mother with serum 25(OH)D concentrations of > 75 nmol/L during pregnancy had an increased risk of asthma at nine years of age, reported Gale et al.[24] Although, another study measured serum 25(OH)D during late pregnancy and concluded that there was no association between maternal vitamin D status and risk of childhood asthma at six years of age.[25] Nevertheless, a Spanish study found no association between maternal vitamin D status during pregnancy and the rate of wheeze or asthma. But they did report an inverse association with the risk of respiratory infection.[26]

Data from a birth cohort study from Perth, Australia revealed that low serum 25(OH)D levels at the age of 6 were prognostic of atopy or asthma associated phenotypes in boys at 14 years old.[27] In Italy, a study of children with asthma constituted that 53,3% of the children surveyed were vitamin D deficient and had serum 25(OH)D levels less than 20 ng/mL. Lower vitamin D levels were related to worse asthma control and lower lung function.[28] In another cross-sectional study from North America, 17% of children with asthma were vitamin D deficient and there was a significant correlation between vitamin D levels and lung function and markers of atopy such as IgE levels.[29]

Pathogenesis

The first study which demonstrated a relation between vitamin D levels, lung function and structural changes in vivo was from Gupta et al. He measured serum 25(OH)D levels from children with moderate and steroid resistant asthma, and non-asthmatic children. They discovered that serum 25(OH)D levels were lowest in children with steroid resistant asthma.[30] Also, the authors reported reduced lung function, increased corticosteroid use and asthma exacerbations with lower vitamin D levels in asthmatic children. Even more important was that they found that low vitamin D levels were associated with an increase in airway smooth muscle (ASM) mass in children with steroid resistant asthma.
In vitro studies support the role of vitamin D in airway remodeling. Increased proliferation of ASM (airway smooth muscle) cells exposed to serum from asthmatic patients is inhibited by

1,25(OH)2D.[31] Damera et al. demonstrated that 1,25(OH)2D can inhibit ASM cell proliferation in both normal and asthmatic subjects by preventing cell cycle progression.[32] In vivo and in vitro animal studies support an important role for vitamin D in modulating normal lung development, such that vitamin D deficiency impairs lung growth.[33][34]

The role of vitamin D on T-cell responses has been well studied. T-cells, particularly T-helper (Th) 2 cells can play a role in the pathogenesis of asthma through the production of cytokines, such as IL-4, IL-5, IL-9 and IL-13.[35] Secretion of these cytokines is essential for the class switching of B-cell to immunoglobin (Ig) E synthesis, the recruitment of mast cells and the maturation of eosinophils.[36] It is well established that 1,25(OH)2D inhibits Th1 cytokine production.[37] However, Pichler et al. found that 1,25(OH)2D can also inhibit both Th1 and Th2 cytokine production from human cord blood T cells.[38]

Exacerbation

Much of the burden of asthma comes from the severe asthma exacerbations that require hospitalization.[35] Higher levels of vitamin D are associated with fewer asthma exacerbations in asthmatic children between 6 and 14 years old, according to a study from Costa Rica. This was determined by a decrease in hospitalizations, emergency department visits, lower IgE, eosinophil counts and inhaled steroid use.[39] In North American asthmatic children, a study of serum vitamin D levels and the subsequent development of severe asthma exacerbations over a 4-year period, confirmed these findings from the Costa Rican study.[40] These studies showed that vitamin D levels less than 30 ng/mL were associated with a higher chance of asthma exacerbations. Besides, children who were vitamin D deficient, had an increased risk of exacerbation, regardless of whether they did or did not receive inhaled steroids, in comparison with children who received inhaled steroids, and had acceptable levels of vitamin D. This indicates a role of vitamin D in intensifying steroid responsiveness.
Vitamin D deficiency may provide for asthma exacerbations by reducing steroid responsiveness. An inverse correlation in asthmatic children between corticosteroid use and vitamin D levels was stated by Searing and colleagues.[29]

Inhaled corticosteroids have a protective effect on severe asthma exacerbations and inhibit the synthesis of Th2 cytokines, which are involved in asthma pathogenesis, and activate IL-10, an anti-inflammatory cytokine in airway epithelial cells. Since severe asthmatics are less responsive to corticosteroids compared with mild asthmatics, corticosteroid insensitivity may be a mechanism contributing to asthma severity.[41] Patients with severe therapy-resistant asthma, following corticosteroid exposure, do not have an increase in IL-10. Nevertheless, the administration of vitamin D may overcome this deficiency in IL-10 production.[42] Studies have revealed that stimulation of ASM cells with VDR ligand, 1,25(OH)2D, control the expression of the genes coding for glucose-6-phosphate dehydrogenase and 1ß-hydroxysteroid dehydrogenase type 1 enzyme, which are both responsible for corticosteroid activation.[43]

Supplementation

Recently, a randomized VIDA trial was published. They randomized 408 adults with poorly controlled asthma to high-dose cholecalciferol or placebo. No significant differences were found in the outcomes of this study, including treatment failure or time to first exacerbation. In a research analysis of patients who responded to vitamin D therapy with a lift in serum 25(OH) vitamin D level >30 ng/ml, had an overall lower rate of treatment failure and exacerbations compared to the placebo group. [44]
One study from Japan randomized 430 children to 1200 IU of vitamin D3 or placebo. They found that children that were randomized to active treatment had an 8% risk reduction in influenza A infection, to the placebo group. Approximately a quarter of these children had asthma, but those who were randomized to cholecalciferol did have fewer asthma exacerbations than children without asthma who received a placebo. [45]
Furthermore, a study from Finland brought to light that vitamin D supplementation in the first year of life was associated with an increased currency of asthma at 31 years of age.[46]
Chen et al. demonstrated the effect of different doses of vitamin D supplementation in rats. They demonstrated with an appropriate dose of 25(OH)2 D3 in early life that supplementation could improve pulmonary function and reduced eosinophil cell infiltration in the airways of asthma rats.[47]

Conslusion/discussion

Much of the data support the previously mentioned hypothesis that higher vitamin D levels lead to better asthma outcomes. However, vitamin D deficiency is often an indirect marker of other confounding factors such as physical activity, making it hard to determine an association between vitamin D status and asthma.

If we look at the onset of asthma, several studies found no association between maternal vitamin D intake during pregnancy and the risk of asthma in children. Only one study found a relation between low vitamin D levels during pregnancy and a higher risk of wheezing or asthma in children. But the conflicting of this all, is the study which found a higher risk of asthma at 9 years old if the mother had >75 nmol/L (>30ng/ml) vitamin D levels during pregnancy.
Several studies that were conducted in children found a relation between low levels of vitamin D and worse asthma control and lung function. And one study found that low vitamin D levels at the age of 6, were prognostic of asthma at the age of 14. The evidence suggests that maternal vitamin D intake during pregnancy has not much of an association with the risk of developing asthma in children. But low vitamin D levels at an early age in children do have impact on asthma control and lung function later in life. The evidence that suggests that higher 25(OH)D levels reduce the incidence of asthma is conflicting and there is yet to be a study with high methodological quality, that convincingly demonstrates that vitamin D deficiency is implicated in the onset of asthma.

The expression of the CYP27B1 and VDR genes by macrophages, T lymphocytes, and dendritic cells suggests that the immune system could be a target for the effect of vitamin D. In the study with Costa Rican children, low 25(OH)D levels were associated with high IgE and eosinophil counts, as well as increased asthma-related hospitalizations and the use of anti-inflammatory medication. Nevertheless, an association does not mean that it is the cause of it. There are several factors that could influence the relationship between vitamin D levels and asthma development. Such as the fact that people with asthma spend more time indoors, are less physically active, and therefore do not get enough sunlight.

The results with supplementation suggest that supplementation is only beneficial if the level of vitamin D is successfully raised. Based on the concept of serum vitamin D levels being an assistant of inflammation, is that the study subjects with less severe asthma were more likely to respond to supplementation. However, these findings are important because they suggest that a vitamin D dosage administration based on a targeted serum 25(OH)D level may be better than a fixed-dosage administration. Also, this study was conducted in adults, while the strongest evidence for vitamin D and asthma was attended in studies with children. The study from Finland, which demonstrated the fact that vitamin D supplementation early in life, was correlated with an increase of asthma currency at the age of 31. This suggests that vitamin D supplementation definitely has an effect when taken early in life. The data from the study with ligand stimulation and the control of the activation of corticosteroids, suggest that

vitamin D supplementation could be used as an extra therapy to overcome steroid resistance in severe asthma. Also, I think it is important that serum 25(OH)D concentrations are measured more than once during the studies, because it is known that vitamin D levels vary over seasons, and likely over time. Also, optimal circulating 25(OH)D levels may be much higher than the current recommendations, because these recommendations are based on studies of bone health.

I concluded that vitamin D intake during pregnancy has no association with children developing asthma. But vitamin D has an effect on asthma control and lung function. More factors are responsible for the relationship between vitamin D levels and asthma development. Vitamin D supplementation can be used to increase the response to corticosteroids. Using vitamin D to prevent asthma needs further research. So, vitamin D leads to better asthma outcomes early in life, and supplementation can decrease asthma severity, but only when used as an extra therapy to activate corticosteroids.

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