REVIEW ARTICLE

DOES VITAMIN D DEFICIENCY CONTRIBUTE TO THE SEVERITY OF ASTHMA IN CHILDREN AND ADULTS?

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Role of vitamin D in the health of bones has been well established for over decades. It was known that its deficiency caused rickets in children and osteomalacia in adults. Later it was discovered that these can be corrected by giving vitamin D. Researchers discovered that vitamin D can be synthesized by exposure to sun. Hence it was also named "the sunshine vitamin". As time passed it was observed that low levels of vitamin D were associated with multiple diseases. This sparked the interest of the scientific community to further the research on vitamin D which led to the studies that started associating vitamin D with various diseases like cancers (prostate, colon and breast), autoimmune diseases (rheumatoid arthritis), infectious diseases (tuberculosis, hepatitis B, hepatitis C, HIV), cardiovascular diseases, mental illnesses (schizophrenia), diabetes mellitus (type 1, type 2 and gestational) and allergic conditions like asthma. With time, more studies were carried out relating levels of vitamin D to development of asthma, asthma exacerbations and risk factors leading to development of asthma like respiratory tract infections with positive associations. A number of studies were carried out which tried to explain the possible molecular mechanisms relating deficiency of vitamin D in pathogenesis of asthma. This review summarizes the role of vitamin D in development of asthma and probable mechanisms relating vitamin D to the pathogenesis of asthma.

Keywords: Asthma, Vitamin D, allergic disease

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INTRODUCTION

Asthma is a disease affecting any age group. It is characterized by recurrent wheeze and shortness of breath due to inflammation of airway passages of lungs.[1] Global Initiative for Asthma defines asthma as "Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation".[2] It is one of the major diseases that has great financial and social impact on the economy and environment of a country in the form of utilization of health resources.[3] Lara *et al*., 2011 reported that In USA people with asthma missed 10.5 million days of school and 14.2 million days of work. Similarly there were 1.75 million hospital visits related to asthma and 456,000 hospitalizations due to asthma.[4]

MATERIAL AND METHODS

PubMed and Google scholar were searched with the keywords Asthma, vitamin D, children and adults. The results were then again filtered with year range from 2010 to 2014.

Epidemiology of Asthma:

Research shows that the prevalence of asthma has been on the rise since 1960 and is regarded as an epidemic. It affects 300 million people worldwide. It is projected that there will be an additional 100 million people affected by asthma by 2025. The countries those are farthest away from the equator sharing the major burden of the disease.[5–7] To *et al* in 2012 carried out a survey to find global burden of asthma in adults. They used stratified probability sampling method in 70 countries worldwide to cover 100% of the country's eligible adults of equal to or more than 18 years of age. They based the prevalence of asthma on responses to questions relating to self-reported doctor diagnosed asthma, clinical/treated asthma, and wheezing in the last 12 months. The prevalence of doctor diagnosed asthma in adults was estimated to be 4.3% (95% CI: 4.2; 4.4) globally. It varied considerably in the participating 70 countries from 0.2% in China to 21.0 % in Australia. When less stringent definition of asthma was use then it was seen that clinical asthma (or treated asthma) was 4.5% (95% CI: 4.4; 4.6). It was also noted that the prevalence for clinical asthma also varied among the participating countries. It ranged from 1.0% in Vietnam to 21.5% in Australia. This showed 21 folds variation in global asthma. The prevalence for other countries was Sweden (20.2%), UK (18.2%), Netherlands (15.3%), and Brazil (13.0%). The global prevalence for wheeze was estimated to be 8.6% (95%CI: 8.5; 8.7) when least stringent definition was used. The prevalence of wheeze for different countries was; Australia (27.4%), the Netherlands (22.7%), the United Kingdom (22.6%), Brazil (22.6%), and Sweden (21.6%).This showed that Australia had the highest prevalence. A

fifteen fold variation was observed in the various countries that participated in the survey.[3]

Asthma has become more common in both children and adults around the world in recent decades. The increase in the prevalence of asthma has been associated with an increase in atopic sensitization, and is paralleled by similar increases in other allergic disorders such as eczema and rhinitis according to a report by Global Initiative of Asthma (GINA).[7]

In a report by Lara *et al* it was seen that asthma prevalence in USA was 8.2%. Within the population it was noted that it was higher in females and children compared to males and adults. It was also noted that Puerto Rican race and non-Hispanic Blacks has more asthma as compared to general population. Factors like family income below poverty and residing in Midwest and Northeast regions also had higher prevalence.[4]

The prevalence for current asthma, rhino conjunctivitis and eczema in the 13–14-year age group was 14.1%, 7.3% and 14.6%, respectively worldwide and in the 6–7-year age group the prevalence for current asthma, rhinoconjunctivitis and eczema was 11.7%, 8.5% and 7.9%, respectively.[8] The prevalence of asthma in UK girls in age group 6–7 years and 13–14 years was 23.3% and 21.4% respectively and for boys it was 27.6% and 23.2% respectively. In Irish children prevalence of asthma in age group 6–9 years was 23.7%, whereas in Germany girls in age group 6–7 years and 13–14 years was 12.7% and 19.7% respectively and for boys it was 13.6% and 15.2% respectively.[7–8] In Africa prevalence of diagnosed asthma in children 13–14 years was 14.4%.[10] Asthma prevalence in children at the age of 2–3 years was 14.6%.[11] Overall prevalence of Asthma in South Australia was reported to be 12.2 % in children 2–15 years of age.[12]

In Asia, the mean of asthma ever and current wheeze reported in different countries in children between age 13–14 years were 12.6 (+0.39%) and 8.8 (+0.07%) respectively. Asthma ever and current wheeze reported in different countries in children between age 13–14 years were Bangkok 15.9 % and 13.9 %, Beijing 6.3 % and 7.2 %, Philippines 20.9% and 8.4%, Hong Kong 10.1% and 8.6% respectively.[13] In India and Pakistan the prevalence of clinical asthma was 5 % and for wheezing asthma it was 10%.[3] It has been reported earlier that asthma prevalence is more in children as compared to adults.[4] However in Pakistan data is deficient for the prevalence of asthma in children. Recently, Adeel *et al* conducted a study in Karachi, Pakistan to determine the prevalence and predictors of asthma in children from 3 to 13 years of age. They estimated asthma prevalence to be 10.2% (95% CI: 8.4–12) with male gender and young age group (3–7 years) being more affected.[14]

Vitamin D and Asthma:

Researchers focused on identifying the factors that led to the development of asthma and the cause of rise in its prevalence in developed and developing countries. This led to researches to identify several features common to both asthma and vitamin D deficiency. These included living in cities, obesity and African American ethnic group.[5–6] Studies conducted both in animal models and human foetal tissues suggested a role of vitamin D in growth and maturation of foetal lung.[15] This sparked an interest in the scientific community to conduct more researches on vitamin D deficiency and its role in asthma besides its debatable role in other non-skeletal diseases like cardiovascular, diabetes mellitus, schizophrenia and multiple sclerosis.[16]

The problem of vitamin D deficiency affects the whole globe despite progress in medical field. It is still an epidemic. Vitamin D deficiency or insufficiency is present in over a billion of world's population.[17] When the levels of vitamin D are between 20–29 ng/mL it is considered as vitamin D insufficiency and the patient is said to be vitamin D deficient when its levels are ≤20 ng/mL. A multitude of studies have reported that in USA and Europe more than 40% of the adult population of age more than 50 years is deficient in vitamin D. Whereas, in pre-teen white girls it is about 48%. In adolescent Hispanics and Black American boys and girls vitamin D deficiency is reported to 52% and 32% in young adults. In Tibet and Mongolia vitamin D deficiency was reported to be 60% in infants leading to clinical manifestation of rickets.[18] In Saudi Arabia male subjects of young age (between 25–35 years) had a prevalence of 28% of low vitamin D levels with 10% in the range of deficiency and 18% in the range of insufficiency. In older age group (more than 50 years) the prevalence was 37% with 12 percent being deficient and 25% being insufficient.[19] In children similar trends were noted. At the time of birth 81% of new-borns had vitamin D deficiency. 50% of children ages 1–5 year and 70% of children age 6–11 years had vitamin D deficiency or insufficiency. In India and China it was 30% to more than 50% in children.[20] In Pakistan the National nutritional Survey (NNS 2011) is the first survey in Pakistan assessing Vitamin D deficiency at a large scale via bio-chemical data. In non-pregnant women vitamin D deficiency was found to be 66.8% with 72.5% in urban and 64.3% in rural areas. In pregnant women the prevalence of vitamin D deficiency was 68.9% with 73.5% in urban areas and 67.2% in rural areas.[21]

It was noted that only genetics does not play a role in asthma development but there are other factors from the environment that influence it. One of these factors was dietary vitamin D. Several studies carried

out showed that there was a relationship between vitamin D status and respiratory symptoms. Certain studies showed the role of maternal vitamin D intake and subsequent development of asthma in children. Other studies correlated the development of asthma by immune modulatory action.[22]

Recently Litonjua *et al* conducted a thorough review on possible mechanism of how vitamin D deficiency can play a role in the development of asthma and allergies. It included the role of vitamin D in immune system and function of lung both in utero and during early life. This suggested that vitamin D levels in the mother correlated inversely with the development of asthma in foetus.[23] Two studies showed that in early childhood, allergic rhinitis, recurrent wheeze and asthma were inversely correlated with vitamin D intake of the mothers. However these studies had the limitation of being shorter in duration. Also they did not measure the vitamin D levels during pregnancy and childhood. In another study conducted in Australia shows that vitamin D levels measured at six years of age predicted significantly the development of atopy and asthma in boys at 14 years of age. This study had the limitation of inadequate follow up and vitamin D levels were not measured in the early life. In another study it was shown that children who have deficient vitamin D levels are more at risk for developing respiratory infections. Respiratory infections themselves are thought to be the major contributor to acute asthma exacerbation. This was also established in a large population survey (NHANES III).[24,25] Zosky *et al* conducted a study recently in a longitudinal birth control to measure the association between maternal vitamin D deficiency and asthma status and postnatal lung growth. They suggested that vitamin D deficiency during development of foetal lungs in pregnancy may have an effect on postnatal lung development and may increase the risk of development of lung disease.[26] In another study relationship between vitamin D levels and clinical parameters of asthma were studied in children. The study group included 120 asthmatic children and 74 children as control with no evidence of allergic disease. They found that the vitamin D deficient group had significantly higher severity and total number of exacerbations of asthma along with the need for use of systemic glucocorticoid.[27] Zosky *et al* in another study in 2011 studied the relationship between vitamin D deficiency and changes in lung structure and function in BALB/c mice. They found that vitamin D deficiency was associated with altered lung volumes and functions.[28] This study was the basis for another study conducted in mouse model (using BALB/c mice). They also found that vitamin D deficiency in adult female mice lead to airway remodelling and airway hyper-responsiveness.[29] However again it was surprising to see that only female mice were affected and males were not affected and secondly it was carried out in an animal model which maybe close to human but also different from it. In a systematic review by Zhang *et al* it was noted that the prevalence of vitamin D deficiency was high in asthmatic children. Also vitamin D deficiency was found to be associated significantly with a decrease in lung function of asthmatic children.[30] Despite all these studies a study by Peter *et al* showed different results in adults. They found that although overall serum vitamin D levels were low in adolescents but they did not correlate with the presence of asthma, its multiple characteristics, its morbidity and response to the treatment.[31]

However a study conducted in British children showed that there was a fivefold increase in the risk of asthma at 9 years when maternal serum vitamin D levels were >75 nmol/L (>30 ng/ml) in late pregnancy. This suggested that even vitamin D supplementation could even be a risk factor for asthma and allergic diseases. However this study was limited because of loss to follow up at 9 years and there was no adjustment for confounders.[44] Similarly Morales *et al* conducted a study and they found that vitamin D levels of the mother correlated inversely only with the respiratory infections in the offspring's but they did not correlate with wheeze in age group 1 to 4 years and asthma in age group 4–6 years.[32] Likewise, Camargo *et al* measured vitamin D levels in the cord blood of 922 new-borns. They found that these levels were only associated with respiratory infections and wheeze in early childhood, inversely. However they did not correlated with the incident of asthma at 5 years of age.[33]

Mechanism of the role of Vitamin D in Asthma:

In recent studies relationship between vitamin D receptor polymorphism and asthma is being studied. In one such study conducted by Haifa *et al* it was shown that VDR genotypes *Fok1, Bsm1*and *Taq1* showed significant association with susceptibility to asthma. The polymorphism probably acts by altering the actions of vitamin D and thereby effecting development of asthma and its severity.[34]

Although several studies have tried to find the possible mechanisms relating deficiency of vitamin D to asthma developments however none has so far been able to provide a detailed and clear cut mechanism by which deficiency of vitamin D could lead to asthma development or cause an increase in its severity or frequency.[35] We will review the possible mechanisms that could play a role in asthma aetiology.

One of the possible mechanisms is the down regulation of atopy by vitamin D to control allergic diseases like asthma. This idea sprouted from various

studies that showed that vitamin D has an important role to play in both adaptive as well as innate immunity. A study conducted by Kwok-Ho *et al*., showed that both human and mouse cells can convert calcidiol to calcitriol (active form of vitamin D) via 1 Alpha hydroxylase enzyme. This activation resulted in suppression of proinflammatory and vasodilatory cytokines that were released by mast cells. It also suppressed Ig E mediated mast cell activation.[36] Besides this study other studies also showed that reducing eosinophilia, reducing Ig E levels, increasing T regulatory cells and remodelling of airways also lead to decrease in asthma exacerbations.[5,37] Second mechanism involved innate immunity. It has been known that respiratory infections lead to asthma exacerbations. A study conducted by Debley *et al* showed that exposure to active vitamin D resulted in enhanced secretion of defensive proteins and chemokines in nasal epithelial cells of the asthmatic children thereby decreasing respiratory infections and asthma.[38] Other studies also go in the favour that vitamin D can enhance secretion of defensive proteins like cathelicidin which play an important role in innate immunity by immediately destroying invading pathogens and hence preventing respiratory tract infections.[39] Similarly other studies show that immune cells exposed to mycobacterium tuberculosis or lipopolysaccharides had elevated levels of expression of vitamin D receptor and 1 alpha hydroxylase. This in turn led to increased expression vitamin D. In turn vitamin D increased the expression of genes that synthesized cathelicidin a defensive antimicrobial protein.[5]

Another possible mechanism by which vitamin D can contribute to asthma is by effecting normal lung development. It has been shown both in human foetus cells and animal models that vitamin D is required for normal lung development as well as it maturation. There are also studies that indicate that vitamin D is also important in maintaining a normal lung architecture and function.[5] In a mouse model it was shown that mice born to mothers who had decreased vitamin D levels showed low lung volumes and functions without change in growth.[43] There are also studies that suggest a role of vitamin D in the modification of gene expression of the bronchial smooth muscle thereby affecting its morphology, cell growth and survival and extracellular matrix.[42]

Interestingly it was also seen in some studies that vitamin D levels were associated with steroid use both in adults and in children. Sutherland *et al* conducted a study in 54 non-smoking adults with asthma. They found that low levels of vitamin D were associated with decreased glucocorticoid response suggesting that improving vitamin D levels can improve glucocorticoid response and hence asthma exacerbation.[39] A similar study was conducted by Ann Chen Wu *et al*., in children. It was noted that asthma response to inhaled glucocorticoid correlated positively with lower vitamin D levels.[40] However there are studies conducted both on adults and children that show better results in children as compared to adults.[41]

Studies were conducted to find out how vitamin D acts on the cell and produce its effects. It was shown that once in blood it is bound by vitamin D binding protein. This complex is carried to the target tissues or cells. Once it reaches its target vitamin D enters the cell and binds to its receptor known as vitamin D receptor (VDR). VDR belongs to the superfamily of nuclear receptors (NR). This receptor has two sites for binding, the genomic pocket known as VDR-GP and the other one as alternate pocket (VDR-AP). Vitamin D binds to the genomic pocket. This complex then bind to another set of receptors known as retinoid X receptors (RXR) forming a heterodimer. This then binds to specific sequences on DNA known as vitamin D response elements (VDRE). These VDRE are located near the genes whose expression they control. These activate or suppress the genes located ahead of the depending on the situation. This requires recruitment of co activators or co suppressors for the proper expression or suppression of the genes.[45] For example when calcium levels are low in serum vitamin D is activated. It reaches cells in the intestine where it activates genes that are responsible for the formation of calcium binding protein 9k (**(**$CaBP_{9k}$). This protein increases absorption of calcium from the intestine to increase calcium absorption. This returns calcium to normal levels along with other mechanism that restores calcium levels like increased bone resorption and increase calcium absorption form kidneys. Similarly at cellular level vitamin D induces osteopontin (SSP1), Receptor Activator for Nuclear Factor κ B Ligand (RANKL) and osteocalcin (BGP) to control the remodeling of bone. Likewise it acts similarly at cellular level to modulate the immune system.[45–47]

CONCLUSIONS

There is strong evidence that suggests a causal association between low vitamin D levels and asthma severity and exacerbation along with factors like respiratory infections that lead to asthma. Also there is evidence especially in children that vitamin D level can increase responsiveness of glucocorticoid therapy to control asthma. Several mechanisms have been proposed to explain the relationship between low vitamin D levels and development of asthma. These include role of vitamin D in normal development of lung structure and function, down regulation of atopy. Increased immunity against respiratory infections and

increase responsiveness of glucocorticoid therapy. The data so far suggests that supplementing with vitamin D can decrease development and severity of asthma and exacerbation. So it is suggested to carry out well designed randomized, double blind controlled trials to father the evidence.

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