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Review article

Trends of vitamin D in asthma in the pediatric population for two decades: a systematic review

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Vitamin D exhibits anti-inflammatory properties through multiple mechanisms. Vitamin D deficiency is associated with increased inflammation, exacerbations, and overall worse outcomes in pediatric asthma and is observed in asthmatic children with obesity. In addition, given the increase in the prevalence of asthma over the last few decades, there has been enormous interest in vitamin D supplementation as a potential therapeutic option. However, recent studies have suggested no strong association between vitamin D levels or supplementation and childhood asthma. Recent studies have reported that obesity and vitamin D deficiency are associated with increased asthma symptoms. Thus, this review summarizes the findings of clinical trials regarding the role of vitamin D in pediatric asthma and analyzes the study trends of vitamin D over the past 2 decades.

Key words: Vitamin D, Asthma, Clinical trials, Child, Obesity

Key message

- Vitamin D may affect asthma via multiple mechanisms, including lung and optimal immune system functions.
- Many clinical trials have demonstrated the beneficial effects of vitamin D on asthma onset and aggravation. However, definitive clinical trials are lacking, and reports have detailed contradictory effects of vitamin D in children with asthma.
- Some exciting reports stated that obesity and vitamin D deficiency are associated with increased asthma symptoms in the pediatric population.

Introduction

Asthma is a chronic disorder of the conducting airways characterized by reversible airway obstruction and airway inflammation.[1] Pediatric asthma is a significant concern because it increases the number of hospital visits and economic burden more than asthma in adulthood.[1] So far in the 2000s, asthma prevalence has increased globally over a short period due to the impact of environmental and genetic factors.[2] Previous epidemiological Korean studies reported a 10%–14% prevalence of asthma in children.[3,4]

Vitamin D is essential for calcium and bone metabolism and immunomodulation.[5] Vitamin D may affect asthma and allergy risk via multiple mechanisms. Vitamin D deficiency, one of the increasing causes of asthma, has become more severe globally over the past few decades.[5,6] Recent studies in adults and children have shown a higher prevalence of low vitamin D levels in asthmatics than in the general population.[6,7] Moreover, low vitamin D levels are associated with higher severity of asthma and impaired pulmonary function.[6,7] Asthmatic patients with vitamin D deficiency have shown increased airway hyperresponsiveness and corticosteroid requirements, and vitamin D might increase their response to glucocorticoids.[8] In a prospective study, maternal vitamin D intake during pregnancy was inversely associated with the risk of recurrent wheezing in childhood.[9] However, although many studies have been conducted in Korea and abroad of the relationship between asthma and vitamin D deficiency or insufficiency, the condition has increased worldwide, especially in adolescents and young adults.[10,11]

Recent contradictory results suggest no strong association between serum vitamin D levels or vitamin D supplements and childhood asthma. Thus, this review aimed to summarize published clinical research investigating the effects of vitamin D on the development and aggravation of asthma in children. Here, we critically review the findings of clinical trials regarding the role of vitamin D in pediatric asthma and analyzed the study trends of vitamin D over the past 2 decades.

Study selection and characteristics

PubMed was searched by combining the terms (asthma, pediatric asthma), (vitamin D, 25-hydroxyvitamin D [25(OH)D]), and duration (January 2002 to August 2022) to identify studies reporting research trends in vitamin D and asthma in children. The latest search was performed on August 15, 2022. The search revealed 133 results after the removal of duplicates and elimination of patients aged >19 years. The title and ab-

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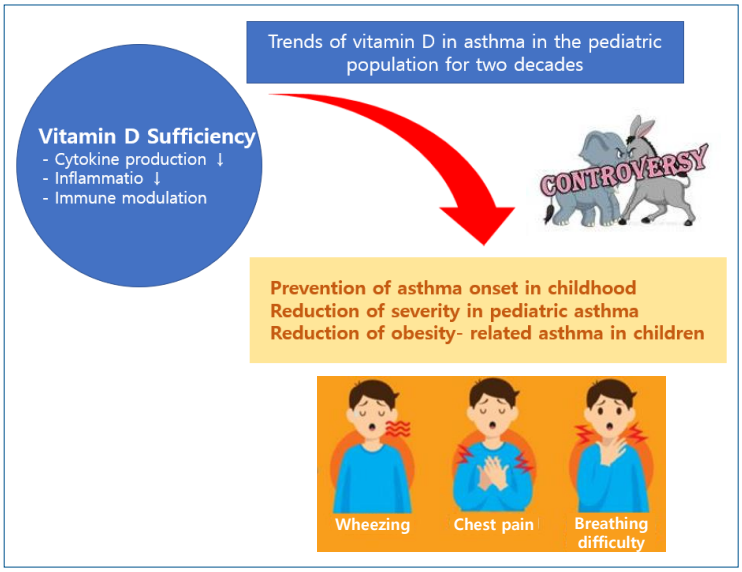

Graphical abstract

stract screening excluded 92 records, while the full-text screening eliminated another 11. Finally, 31 articles were included in this systematic review. The included articles are summarized in Tables 1–3.

Effects of vitamin D prevention on asthma onset in childhood

Several well-established studies have been conducted on this topic (Table 1). Some birth cohort studies demonstrated that serum vitamin D levels at birth and maternal vitamin D status or exposure during pregnancy may affect the incidence of childhood asthma. The association between vitamin D and asthma in children will be summarized from 2 main aspects: serum vitamin D levels before delivery; and cord blood and early infancy supplementation.

Effects of vitamin D levels on asthma onset in childhood

According to Hollams et al.,[12] serum vitamin D levels were assayed in 989 (6-year-olds) and 1,380 (14-year-olds) children from an unselected community birth cohort; of them, 689 were assessed at both ages. Children (particularly males) with inadequate vitamin D levels were at increased risk of developing atopy, bronchial hyperresponsiveness, and asthma.

Owing to the early onset of childhood asthma, we hypothesized that maternal vitamin D status and exposure during pregnancy might play a role in the development of asthma. The subjects' 25(OH)D levels were measured at midgestation and at birth, and airway resistance was measured of the offspring at 6 years of age to clarify the association of maternal and fetal 25(OH)D levels with lung function and childhood asthma.[13] The maternal 25(OH)D levels were not associated with airway resistance in offspring at 6 years of age, but low levels of 25(OH)D at birth were associated with higher airway resistance in childhood.[13]

In a Taiwanese birth cohort study,[14] children aged 0–4 years underwent serum 25(OH)D level measurements 6 times: maternal blood (before delivery), cord blood, and ages 1.5, 3, and 4 years. Specific immunoglobulin E antibodies against food and inhalant allergens were measured 6 times in children (at 6 months and at 1, 1.5, 2, 3, and 4 years). A significant correlation was found between maternal and cord blood 25(OH)D levels and persistently lower vitamin D serum levels in children born to mothers with vitamin D deficiency. Vitamin D deficiency in mothers (<20 ng/mL) appears to be associated with a higher prevalence of allergen sensitization before 2 years of age. Higher maternal 25(OH)D levels were significantly associated with a lower risk of asthma at age 4 years.[14] Additionally, in the Generation R Study,[15] 4,951 mother-child pairs comprised a population-based prospective cohort and underwent blood sampling of maternal (in midgestation) and umbilical cord (at birth). After additional adjustment for the child's 25(OH)D concentrations at 6 years of age, only the associations of 25(OH)D concentrations in midgestation with forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) and forced expiratory flow at 75% at 10 years of age remained.

Vitamin D supplementation during pregnancy and infancy

Vitamin D intake by infants or mothers during pregnancy might play a role in the development of asthma in children (Table 1). In a prospective birth cohort study up to 6 years of age, prevention through modified vitamin D3 supplementation in infancy could reduce the prevalence of allergic diseases.[16]

Table 1. Summary of effects of vitamin D supplementation on asthma onset in children by study included in the systematic review

Study	Design	Subjects	Description
Hollams et al.[12] 2011	Large unselected cohort study Clinical and immunological phenotyping at ages 6 and 14 years	989 (6-yr-olds)/1,380 (14-yr-olds) children: 689 subjects were assessed at both ages	Vitamin D levels at age 6 years were significant predictors of subsequent atopy/asthma-associated phenotypes at age 14 years.
Gazibara et al.[13] 2015	Population-based prospective cohort study during 6 years Serum 25(OH)D levels in midgestation and at birth	3,130 Mothers/ their children	Low 25(OH)D levels at birth were associated with a higher airway resistance in childhood.
Chiu et al.[14] 2015	Birth cohort of children aged from 0 to 4 years Serum 25(OH)D levels in maternal blood before delivery, cord blood, and at ages 1.5, 3, and 4	A total of 164 mother-child pairs	Low maternal 25(OH)D levels appear not only to be associated with an increase in the prevalence of allergic sensitization but also the risk of asthma in early childhood.
Mensink-Bout et al.[15] 2019	A population-based prospective cohort Maternal (midgestation)/umbilical cord (birth) blood At age 10 years, lung function, questionnaire, and inhalant allergic sensitization by skin prick tests	4,951 Mothers/their children	The associations of 25(OH)D concentrations in midgestation with FEV_1/FVC and $FEF_{75\%}$ at age 10 years
Hypponen et al.[17] 2004	The Northern Finland Birth Cohort Vitamin D supplementation during the first year of life Women during pregnancy and their offspring are followed up at ages 1, 14, and 31 years.	Those who attended clinical examination (n=6,007) were compared with those who were not invited or were invited but did not attend (n=5,630).	Association between vitamin D supplementation in infancy and an increased risk of atopy and allergic rhinitis later in life, but not asthma
Bäck et al.[16] 2009	A prospective birth cohort study up to the age of 6 years. The relationship between lower or higher vitamin D3 intake and atopic illness later in childhood was assessed.	123 (6-yr-olds) children	Prevention through modified vitamin D3 supplementation in infancy could reduce allergic diseases.
Goldring et al.[18] 2013	A randomized controlled trial Assessed offspring at 3 years	180 Pregnant women at 27 weeks gestation - No vitamin D (n=60) - Daily 800 IU ergocalciferol (n=60) - Single 200,000 IU bolus of cholecalciferol (n=60)	Prenatal vitamin D supplementation in late pregnancy was not associated with decreased wheezing in offspring at age 3 years.
Grant et al.[20] 2016	A randomized, double-blind, placebo-controlled parallel-group trial Pregnant women (from 27-week gestation to birth) and their infants (from birth to 6 months) Woman/infant pairs: placebo/placebo, 1,000/400 IU, or 2,000/800 IU	A total of 260 mother-child pairs - Placebo (n=87) - Lower dose oral vitamin D (n=87) - Higher dose oral vitamin D (n=86)	Vitamin D supplementation during pregnancy and infancy reduces the proportion of children sensitized to mites at age 18 months. There were study group differences in the proportion of children with primary care visits described by the doctor as being for asthma.
Litonjua et al.[19] 2016	A randomized, double-blind, placebo-controlled trial: (1) parental report of physician-diagnosed asthma or recurrent wheezing through 3 years of age; (2) third trimester maternal 25(OH)D level	881 Pregnant women (from 10 to 18 weeks' gestation) at high risk of having children with asthma - Daily 4,000 IU vitamin D+prenatal vitamin containing 400 IU vitamin D (n=440) - Placebo+prenatal vitamin containing 400 IU vitamin D (n=436)	The incidence of asthma and recurrent wheezing in their children at age 3 years was lower by 6.1%, but this did not meet statistical significance.

25(OH)D, 25-hydroxyvitamin D; $FEF_{75\%}$, forced expiratory flow at 75%; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IU, international unit.

However, in the 31-year Northern Finland Birth Cohort, vitamin D supplementation in infancy did not appear to influence the development of asthma or wheezing in children.[17]

Three randomized controlled trial studies ascertained the role of maternal diet in the risk of asthma development in their offspring. In one trial,[18] 180 pregnant women at 27 weeks' gestation were allocated to receive no vitamin D, 800 IU of ergocalciferol daily until delivery, or a single oral bolus of 200,000 IU of cholecalciferol. Researchers blinded to the allocation assessed the offspring at 3 years of age using a questionnaire, impulse oscillometry, and exhaled nitric oxide. However, no significant difference was found in atopy, lung function, or exhaled nitric oxide between supplemented groups and controls.[19] In another trial,[19] 881 mothers and infants received vitamin D (440 women administered 4,000 IU of vitamin D daily plus a prenatal vitamin containing 400 IU of vitamin D; 436 women administered placebo plus a prenatal vitamin containing 400 IU of vitamin D). The incidence of asthma and recurrent wheezing in

children at 3 years of age was 6.1% lower; however, this result was insignificant. In the other trial,[20] mothers and infants had lower or higher doses of vitamin D (400 IU/800 IU in infants and 1,000 IU/2,000 IU in mothers). Vitamin D supplementation during pregnancy and infancy reduces the proportion of children sensitized to house mites at 18 months of age, and there were study group differences in the proportion of children with primary care visits described by doctors as being for asthma.[20]

In summary, vitamin D supplementation during pregnancy and infancy may prevent asthma onset in childhood, but this remains controversial.

Effects of vitamin D and asthma severity in pediatric asthma

Over the past 2 decades, several research groups have focused on the role of vitamin D in asthma pathogenesis. Subsequent studies identified a link between vitamin D deficiency and an overall worse outcome of lung function, symptom control, and exacerbation in children with asthma (Table 2).

Vitamin D levels and pediatric asthma

Brehm et al.[7] assayed serum vitamin D levels in 616 children with asthma; lower vitamin D levels were associated with increased asthma severity. In addition, vitamin D deficiency was higher in asthmatics than in controls, while vitamin D sufficiency was lower in asthmatics than in controls.[21,22] In asthmatic children, 25(OH)D was positively correlated with FEV_1 and FEV_1/FVC in the 2 studies,[21,23] but it remained controversial whether asthmatics had a much lower 25(OH)D level than healthy controls.[23] In the age-, sex-, and ethnicity-matched

Table 2. Summary of the effects of vitamin D on asthma severity in pediatric patients by study included in the systematic review

Study	Design	Subjects	Description
Brehm et al.[7] 2009	Cross-sectional study Hospitalization/use of anti-inflammatory medications in the previous year	616 Children with asthma (aged: 6–14 years)	Lower vitamin D levels are associated with increased markers of allergy and asthma severity.
Alyasin et al.[21] 2011	Case-control study and cross-sectional study Serum vitamin D level, pulmonary function test, and eosinophil counts were examined	50 Childhood asthmatics & 50 healthy controls (aged: 6–18 years)	25(OH)D was significantly lower in asthmatic patients than controls and positively correlated with FEV_1 and FEV_1/FVC. No correlation with eosinophil counts, asthma duration, number of hospitalizations, or unscheduled
Chinellato et al.[23] 2011	Case-control study and cross-sectional study Serum vitamin D level, pulmonary function test, and exercise challenge test were examined.	45 Asthmatic & 59 healthy children (aged: 9–11 years)	No significant difference in the 25(OH)D level between the 2 groups. 25(OH)D positively correlated with FVC and FEV_1 but negatively with exercise induced bronchoconstriction.
Maalmi et al.[22] 2012	Case-control and cross-sectional study Vitamin D, Th1, Th2, Th17, Treg, and pulmonary function test	39 Children with controlled asthma/30 controls (aged: 6–16 years): age- and sex-matched	Vitamin D deficiency was higher in asthma compared to control; vitamin D sufficiency was lower in asthma than control. Th1/Th2 ratio and CD25(þ) Foxp3(þ) Treg cells were positively related to 25(OH) D level while IL-17 was negatively correlated.
Ehlayel et al.[24] 2011	Case-control study and cross-sectional study Serum vitamin D level and IgE	483 Asthma & 483 controls (aged: <15 years): age, gender & ethnicity matched	25(OH)D levels were significantly lower, and IgE significantly higher in cases than in controls, with a negative correlation evident. Vitamin D deficiency was the strongest predictor of asthma.
Dabbah et al.[26] 2015	Cross-sectional study Methacholine challenge test/FeNO) Serum vitamin D, total IgE, blood eosinophil counts	71 Nonobese children with asthma (aged: 6–18 years)	No correlation was found between vitamin D level and response to the methacholine challenge test, FeNO, IgE levels, eosinophil counts.
Han et al.[25] 2017	Using data from the National Health and Nutrition Examination Survey from 2001 to 2010	Current asthma or wheeze in 10,860 children (6–17 years)/ 24,115 adults (18–79 years) Lung function in a subset of participants	Positive correlation between vitamin D insufficiency (<30 ng/mL) and current asthma or current wheeze in children and adults Children with asthma (n=1,192) were likelier to have a higher BMI *z* score and a lower serum vitamin D level.
Gupta et al.[28] 2011	Case-control and cross-sectional study 25(OH)D, asthma control test, spirometry, corticosteroid use, and exacerbations were assessed. Fiberoptic bronchoscopy, bronchoalveolar lavage, and endobronchial biopsy (severe, therapy-resistant asthma)	36 Children with steroid-resistant asthma, 26 with moderate asthma, and 24 healthy controls (aged: 6–16 years)	25(OH)D levels were significantly lower in steroid-resistant asthma than either mild asthmatics or controls and inversely correlated with airway smooth muscle mass, bronchodilator response and IgE but positively correlated with asthma control, FEV_1 and FVC. Low 25(OH)D was correlated with asthma exacerbation and medication usage
Brehm et al.[29] 2012	Case-control and cross-sectional study Serum vitamin D level, pulmonary function test, and specific IgE	287 Asthmatic/ 273 healthy children (aged: 6–14 years).	No significant difference in 25(OH)D between cases and controls Lower 25(OH)D correlated with severe asthma exacerbation, atopy, and a lower FEV_1/FVC in cases

(Continued)

Table 2. Summary of the effects of vitamin D on asthma severity in pediatric patients by study included in the systematic review (Comtinued)

Study	Design	Subjects	Description
Turkeli et al.[30] 2016	Case-control and cross-sectional study	102 Preschool children with asthma/102 healthy controls in winter (aged: 1–4 years)	The frequency of vitamin D deficiency and insufficiency was higher in children with asthma, compared to the controls. In the vitamin D-sufficient group, total number of exacerbations during the previous year was much lower compared to the vitamin D-insufficient group.
Yoseph et al.[34] 2015	Double-blind, randomized, placebo-controlled trial Methacholine challenge test, skin prick tests, FeNO, and exhaled breath condensate collection	Children with mild asthma, PC_{20}-FEV_1 <16 mg/mL, and vitamin D <30 ng/mL for 6 weeks of treatment - Oral vitamin D 14,000 in 2-mL units once weekly - Placebo (2 mL of olive oil)	No difference could be demonstrated between the effect of vitamin D and placebo
Jensen et al.[31] 2016	Double-blind, randomized, placebo-controlled trial Serum 25(OH)D: baseline, 10 days, 3/6 months	22 preschool-aged children with asthma - 100,000 IU vitamin D3 (intervention)/placebo (control) - Followed by 400 IU vitamin D3 daily for 6 months	Following 100,000 IU vitamin D3, all children reached serum 25OHD ≥75 nmol/L (>30 ng/mL), compared with half who received placebo.
Tachimoto et al.[32] 2016	Double-blind, randomized, placebo-controlled trial Childhood asthma control test scores at 2, 6 months.	Japanese schoolchildren with asthma - Vitamin D3 supplements (800 IU/day) with placebo for 2 months	Low-dose, short-term vitamin D supplementation in addition to standard treatment may improve levels of asthma control in schoolchildren.
Kerley et al.[33] 2016	Double-blind, randomized, placebo-controlled trial Assessments were completed at baseline and after 15 weeks of supplementation.	Caucasian 51 children from 44 urban (aged: 6–16 years) - Vitamin D supplementation (2,000 IU/day)	Vitamin D3 supplementation led to a significant decreased school days missed. There were nonsignificant, advantageous changes in the placebo group compared with the vitamin D3 group in subjective asthma control and lung function, particularly percentage of predicted FEV_1.
Alansari et al.[35] 2017	Randomized, controlled trial	Children with moderate-to-severe asthma and vitamin D levels<25 ng/mL for 12 months (aged: 2–14 years) - IM+ Oral group (n=116): 400 IU/d + 300,000 IU (IM, <5 years) or 600,000 IU (IM+ oral, >5 years) - Oral-only group (n=115) : 400 IU/day	Rapid compared to maintenance vitamin D supplementation for children with the lowest levels resulted in short- but not long-term reduction in asthma exacerbations.
Kalmarzi et al.[39] 2020	Interventional study Serum levels of 25(OH)D, asthma severity and pulmonary function tests before and after therapeutic prescription of vitamin D	68 Asthmatic children - Vitamin D levels <10 ng/mL: 800-IU capsules (#4) a day for 12 weeks or 50,000-IU tablets (#1) a day for up to 6 days at secondary care level: cholecalciferol 300,000-unit ampoules once a month for 3 months - Vitamin D levels: 10–30 ng/mL: Vitamin D was administered based on the patient's calcium level	Therapeutic prescription of vitamin D is very effective in improving the clinical status of asthmatic children.
Forno et al.[37] 2020	Double-blind, randomized, placebo-controlled trial Pulmonary function test Asthma Control Test (≥12 years)/Childhood ACT (<12 years)	400 with low-dose inhaled corticosteroids and serum 25(OH) D levels <0 ng/mL (aged: 6–16 years) - Vitamin D3, 4,000 IU/d (n=96) - Placebo (n=96) for 48 weeks Maintained with fluticasone propionate	Among children with persistent asthma and low vitamin D levels, vitamin D3 supplementation, compared with placebo, did not significantly improve the time to a severe asthma exacerbation. The findings do not support the use of vitamin D3 supplementation to prevent severe asthma exacerbations in this group of patients.
Thakur et al.[38] 2021	Double-blind, randomized, placebo-controlled trial Childhood asthma control test scores at 12 weeks FEV_1, FeNO, asthma exacerbations, use of systemic steroids, number of emergency visits, postintervention vitamin D levels, and adverse outcomes	60 Children with moderate persistent asthma and placebo (n=30) (aged: 6–11 years) - 2,000 IU per day of vitamin D	Vitamin-D supplementation as an adjunct to standard treatment does not improve asthma control in children.

25(OH)D, 25-hydroxyvitamin D; $FEF_{75\%}$, forced expiratory flow at 75%; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; IU, international unit; Treg, regulatory T cells; PC_{20}, provocation concentration of methacholine required to induce a 20% decrease in FEV_1.

case-control studies, 25(OH)D levels were significantly lower, while immunoglobulin E levels were significantly higher in cases than in controls with a negative correlation evident.[24] According to the National Health and Nutrition Examination Survey in the United States, from 2001 to 2010, there was a positive correlation between vitamin D insufficiency (<30 ng/mL) and current asthma or wheezing in children (Table 2).[25]

However, in a study of nonobese asthmatic children currently not receiving anti-inflammatory treatment,[26] although the mean vitamin D was 23 ng/mL, no correlation was found between vitamin D level, airway reactivity, and airway inflammation.[26] Furthermore, in a population-based cohort of adults, serum 25(OH)D level was positively associated with FEV_1 and FVC and negatively associated with fraction of exhaled nitric oxide (FeNO); these associations disappeared after the adjustment for confounders, including body mass index (BMI).[27] Thus, 25(OH)D levels were not associated with lung function or airway inflammation in nonobese adults.[27]

Vitamin D level and pediatric asthma exacerbation

Several studies have emphasized a link between vitamin D levels and asthma exacerbation in children.[28-30] In the analysis of 25(OH)D levels in 36 children with steroid-resistant asthma, 26 with moderate asthma, and 24 healthy controls, 25(OH)D levels were significantly lower in the steroid-resistant asthma group than the other 2 groups.[28] Low 25(OH)D levels were correlated with asthma exacerbation and medication usage.[28] In another study,[29] no significant difference in 25(OH)D levels was observed between 287 asthmatic children and 273 controls, but a lower 25(OH)D level was correlated with severe asthma exacerbation. Additionally, an analysis of 25(OH)D levels in preschoolers with asthma versus healthy controls showed a significant decrease in serum vitamin D levels in the asthmatics. The total number of exacerbations during the previous year was much lower in the vitamin D-sufficient group than in the vitamin D-insufficient group. The number of children with controlled asthma was also higher in the sufficient group, suggesting a positive correlation between serum vitamin D level and asthma control.[30]

Effects of vitamin D supplementation on clinical outcomes in pediatric asthma

Interestingly, few clinical trials have examined the effects of vitamin D supplementation on clinical outcomes in children with asthma. A double-blind randomized placebo-controlled trial examined whether a 100,000 IU dose of supplemental vitamin D could rapidly increase serum 25(OH)D levels in preschoolers with asthma. At 3 months, all children in the intervention group versus only approximately 50% of the control group had serum 25(OH)D levels >30 ng/mL.[31]

In a study of Japanese children with asthma, an assessment of the frequency and severity of asthmatic episodes was improved by the administration of vitamin D_3 supplements (800 IU/day) for 2 months.[32] In a trial of Caucasian children who received 2,000 IU/day of vitamin D for 15 weeks, supplementation significantly decreased the number of missed school days. However, there were no other positive changes in asthma parameters compared to those in the placebo group.[33]

In a double-blind randomized placebo-controlled trial,[34] children with mild asthma, a provocation concentration of methacholine required to induce a 20% decrease in FEV_1<16 mg/mL, and a vitamin D level<30 ng/mL, the oral vitamin D group received oral vitamin D 14,000 once weekly. Despite significant increases in blood vitamin D levels, no difference was found in the effects of vitamin D and placebo.

In another trial,[35] children with moderate-to-severe asthma and a vitamin D level < 25 ng/mL were randomized to receive vitamin D as a loading dose or for 12 months. Alansari et al.[35] examined the effects of 300,000 or 600,000 IU of vitamin D2 injected as a loading dose followed by 400 IU of oral vitamin D3 daily versus oral therapy only in 231 children (aged 2–14 years).[35] The loading dose versus maintenance vitamin D supplementation in children with the lowest levels resulted in short- but not long-term reductions in asthma exacerbations.[35]

Additionally, the World Allergy Organization reported in 2016 that, based on currently available evidence, it did not support the hypothesis that vitamin D supplementation reduces the risk of developing allergic diseases, including asthma, in children. The panel suggested not administering vitamin D to pregnant women, breastfeeding mothers, or healthy infants in an effort to prevent the development of allergic diseases.[36]

Two recent double-blind randomized placebo-controlled trials support this recommendation.[37,38] Among children with persistent asthma and low vitamin D levels, vitamin D3 supplementation versus placebo did not significantly improve the time to severe asthma exacerbation, and vitamin D supplementation as an adjunct to standard treatment did not improve asthma control in children.[37,38] However, a recent interventional study of 68 asthmatic children found that asthma severity, FEV_1, FVC, and FEV_1/FVC indicators were significantly increased after vitamin D supplementation.[39]

In summary, evidence from the highlighted studies demonstrated an association between vitamin D supplementation and clinical outcomes of pediatric asthma; however, reports from recent clinical trials are inconclusive. More prospective research is needed to clarify whether vitamin D supplementation relieves symptoms associated with asthma.

Vitamin D and obesity-related asthma in children

The prevalence of obesity in children has increased signi-

ficantly since the coronavirus disease 2019 pandemic due to losses of daily routines.[40] Adipose tissue may act as an endocrine organ releasing soluble factors, and excess adipose tissue predisposes an individual to an enhanced inflammatory state and may contribute to the pathogenesis and aggrevation of asthma.[41] Two recent retrospective cohort studiesanalyzed big data for 150,000 subjects.[42,43] One study was divided into 3 groups (aged 2–6 years, 7–11 years, and 12–17 years); before 12 years of age, females had a higher risk for obesity-related asthma; however, after 12 years of age, obese males had a higher asthma risk.[42] Overall, obesity was a major preventable risk factor for pediatric asthma in 2 studies. Therefore, obesity may substantially contribute to childhood asthma morbidity and healthcare costs.

Recent exciting reports stated that obesity and vitamin D deficiency are associated with increased asthma symptoms[25] and that vitamin D supplementation could decrease asthma aggravation in children.[44] There are several well-established studies on this topic (Table 3). Epidemiological studies have reported low serum 25(OH)D levels in children with difficult-to-treat asthma irrespective of body weight. According to a nationwide study using National Health and Nutrition Examination Survey data, children with asthma (n=1,192) were likelier to have a higher BMI z score and a lower serum vitamin D level.[25] Low serum vitamin D (25(OH)D) levels were reported in children with asthma or who were obese, making children who have both asthma and obesity particularly at risk for a low vitamin D level.[28,45] A population-based cohort study found that a 25(OH)D level > 10 nmol/L was associated with 0.46% predicted higher FEV, a 0.46% predicted higher FVC, and a 0.24 ppb lower FeNO level in obese adults with a BMI ≥ 30 kg/m^2.[27] Thus, higher 25(OH)D levels were associated with better lung function and lower airway inflammation in an obese subject.[27] Turer et al.[45] observed that 79% of children who were overweight (BMI 85th–95th percentile for age and sex) and 86% of children with obesity (BMI ≥95th percentile) met the criteria for vitamin D insufficiency (serum vitamin D measured as 25(OH)D <30 ng/mL).

In a study examining vitamin D levels in 235 children with asthma, only 76 were considered obese, and the mean serum 25(OH)D level was 20.6 ng/mL (interquartile range, 13.5–26.0 ng/mL).[46] Children with asthma and a low serum 25(OH)D level are predisposed to worse asthma outcomes. Lautenbacher et al.[47] reported that vitamin D deficiency was associated with pulmonary function decline among obese children of Hispanic and African-American descent but not their healthy-weight controls. In another study, Bose et al.[48] showed a relationship between indoor air quality, asthma, and vitamin D levels in obese children in an urban environment. Three-way interaction models demonstrated significantly greater fine particular matter-associated effects on daytime asthma symptoms only among obese children with low 25-OH D levels. They observed that higher serum 25(OH)D levels mitigated the effects of increased indoor air pollution.[48]

It has been hypothesized that vitamin D supplementation may benefit this patient population. A Cochrane review noted that the dose of vitamin D supplementation for asthma (and, therefore, obesity-related asthma) remains uncertain.[49] A study comparing vitamin D bioavailability in normal-weight versus obese adults attributed decreased vitamin D levels to the deposition of vitamin D in body fat compartments.[50] However, data on vitamin D pharmacokinetics in children with obesity are lacking. Thus, addressing this critical gap in our understanding of vitamin D pharmacokinetics is an essential first step in investigating the role of vitamin D as a treatment for pediatric obesity-related asthma.

In summary, there is ample evidence that both asthma and obesity are inflammatory conditions associated with decreased

Table 3. Summary of vitamin D and obesity-related asthma in children by study included in the systematic review

Study	Design	Subjects	Description
Turer et al.[45] 2013	Cross-sectional study (the 2003–2006 National Health and Nutrition Examination Survey) Age- and gender-specific BMI-percentile cut point	12,292 Children (aged: 6–18 years) - 79% of children with overweight (BMI 85th–95th percentile for age and gender) - 86% of children with obesity (BMI≥ 95th percentile)	Compared with healthy-weight children, overweight, obese, and severely obese children had significantly greater adjusted odds of vitamin D deficiency. Vitamin D deficiency is highly prevalent in overweight and obese children.
Lautenbacher et al.[47] 2016	Cross-sectional study Pulmonary function test, serum vitamin D and cytokines	72 Obese and 71 normal-weight Hispanic and African-American children with asthma recruited at an urban children's hospital (aged: 7–11 years)	Vitamin D deficiency was associated with pulmonary function deficits among obese children, but not among normal-weight children with asthma, an association that was independent of Th1 and Th2 serum inflammatory measures.
Reinehr et al.[46] 2018	NIKI cohort Multicenter study between 2013 and 2016	235 Children (60% boys, age 9.3±1.7 years) with obesity, ADHD, BA, and AD 3,352 children from a healthy population	Vitamin D concentrations were not lower in children with obesity, ADHD, BA, and AD compared to healthy children. Vitamin D levels were not linked to the severity of asthma measured as FEV_1.
Bose et al.[48] 2019	Longitudinal cohort study Indoor $PM_{2.5}$, serum 25(OH)D levels and asthma symptoms	120 Children with physician-diagnosed asthma (aged: 5–12 years)	Among obese urban children with asthma, low vitamin 25(OH)D enhanced adverse respiratory effects associated with indoor $PM_{2.5}$. 25-OH D was protective against asthma symptoms in high $PM_{2.5}$ environments.

BMI, body mass index; ADHD, attention deficit/hyperactivity disorder; BA, bronchial asthma; AD, atopic dermatitis; FEV_1, forced expiratory volume in 1 second; $PM_{2.5}$, particulate matter 2.5; 25(OH)D, 25-hydroxyvitamin D.

serum 25(OH)D levels and that vitamin D supplementation may decrease the inflammatory properties of both diseases.

Conclusion

The incidence and socioeconomic burden of asthma has been increasing among children and adolescents in Korea and other countries. The role of vitamin D in asthma pathogenesis has been a topic of debate for the past 2 decades. This systematic review evaluated the relationship between asthma and vitamin D levels in children. Unfortunately, protocols (duration and dosage) varied among the birth cohorts and double-blind randomized placebo-controlled trials. These clinical trials are not without limitations. Thus, future research must identify the optimal dose and duration of vitamin D supplementation for distinct groups based on sex, ethnicity, age, BMI, and asthmatic phenotype, since all these factors affect vitamin D absorption and bioavailability. Additionally, it is important to determine whether these observations reflect long-term effects on immune regulation.

Footnotes

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