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Serum 25-Hydroxyvitamin D is Associated with Enhanced Pneumococcal Antibody Levels in Individuals with Asthma

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Abstract

Recent studies suggest that vitamin D modulates innate immunity and reduces the risk of microbial infections. Little is known the role of vitamin D in anti-pneumococcal immunity in individuals with asthma. We determined the correlation between serum 25-hydroxyvitamin D (25(OH)D) levels and pneumococcal antibody levels in individuals with asthma, atopic dermatitis or allergic rhinitis, and atopic sensitization status.

A cross-sectional study was conducted for 21 subjects with asthma and 23 subjects without asthma. Pearson's correlation coefficient between serum 25(OH)D levels and the number of positive serotype-specific antibody levels was calculated among individuals with and without asthma, atopic dermatitis and/or allergic rhinitis, and atopic sensitization status. The overall correlation between serum 25(OH)D and the number of positive pneumococcal antibody levels in all subjects regardless of asthma was not significant ($r = -0.14$, $p = 0.38$). Stratified analysis results showed that there was a positive correlation between serum 25(OH)D and the number of positive pneumococcal antibody levels in asthmatics ($r = 0.45$, $p < 0.05$) and an inverse correlation was observed in non-asthmatics ($r = -0.53$, $p < 0.05$). These trends were similar for subjects with and without atopic dermatitis and/or allergic rhinitis ($r = 0.58$, $p = 0.008$ vs. $r = -0.63$, $p = 0.001$).

Despite similar trends in the correlation among those with and without atopic sensitization status ($r = 0.27$, $p = 0.19$ vs. $r = -0.41$, $p = 0.08$), they did not reach statistical significance. 25(OH)D may enhance humoral immunity against *S. pneumonia* in subjects with atopic conditions but not without atopic conditions. Atopic conditions may have an important effect modifier in the relationship between serum 25(OH)D levels and immune function.

Keywords

Asthma; allergic rhinitis; atopic dermatitis; atopy; pneumococcal antibody; Vitamin D; 25(OH)D

Vitamin D deficiency or insufficiency is relatively common and yet a significant public health problem.^{1–4} In the United States, Ginde et al reported a marked decrease in serum 25-hydroxyvitamin D(25(OH)D) levels from 1988–1994 to 2001–2004.⁵ The effects of serum vitamin D deficiency or insufficiency on health outcomes at a population level are yet to be determined. Recent data suggests that 1,25(OH)₂D may regulate innate immune function by the altering cathelicidin (antimicrobial peptide) expression, which, in turn, might reduce microbial infections.^{6–9} However, little is known about the role of vitamin D status in altering adaptive immune functions such as serotype-specific pneumococcal polysaccharide antibody responses. A recent study suggested a potential association between duration of sun exposure and risk of invasive pneumococcal disease.¹⁰ However, the correlation between vitamin D status assessed by measuring serum 25(OH)D levels and pneumococcus-specific immune responses, such as serotype-specific pneumococcal antibody levels, has not been assessed. Therefore, determining the correlation between serum 25(OH)D levels and serotype-specific pneumococcal antibody responses is important given the concerns about *S. pneumoniae* as a significant public health threat.

In addition, even if pneumococcal polysaccharide is considered a T cell-independent type II antigen (TI-2), individuals with defect in T-cell development such as atopic or asthmatic individuals (i.e., Th2 immune profile) might have suboptimal pneumococcal antibody responses because TI-2 antigen still needs T-B cell interactions for optimal antibody response.^{11, 12} Th2-cytokines directly and indirectly (reciprocal inhibition of Th1 activity) reduce antibody responses to pneumococcal antigens.^{12, 13} Indeed, we recently reported the similar inverse correlation between Th2-predominant immune responses (ratio of IL5/IFN- γ secretion after PBMC stimulations with house-dust mite) and serotype-specific pneumococcal antibody levels.¹⁴ Importantly, like others, we observed that the inverse correlation between Th2-predominant immune response and serotype-specific pneumococcal antibody levels was significantly modified by clinically defined asthma status.^{15, 16}

We reasoned that vitamin D status, determined by measuring serum 25(OH)D levels, might influence serotype-specific pneumococcal antibody levels in individuals with asthma or atopy who exhibit defective T-cell development. Addressing this question could clarify the inconsistent effects of vitamin D status and serum 25(OH)D on immune functions.^{17–19} Therefore, we assessed whether serum 25(OH)D levels are correlated with the number of positive serotype-specific pneumococcal antibody levels and whether the correlation is modified by asthma, atopic dermatitis or allergic rhinitis, or atopic sensitization status.

METHODS

Study design

The study was designed as a cross-sectional study that assessed the correlation between serum 25(OH)D levels and the number of positive pneumococcal antibody levels. In addition, we examined whether the correlation was modified by asthma, atopic dermatitis and/or allergic rhinitis, or atopic sensitization status by performing stratified analysis. The study was approved by the Institutional Review Boards at Mayo Clinic.

Study subjects

Study subjects were a convenience sample of 21 patients with asthma and 23 patients without asthma who received medical care at Mayo Clinic in Rochester, Minnesota. We applied the same enrollment and exclusion criteria as our previous study (non-Olmsted County residents, no research authorization) for using medical record for research.^{20–22} Briefly, the exclusion criteria were as follows: 1) the exclusion criteria for a previous longitudinal Finnish study²³ (moderate or severe disability; cerebral palsy; syndromes and nasopharyngeal disorders affecting swallowing; ear, nose, throat disorders affecting the anatomy of the nose and pharynx; documented or suspected immune deficiency; and immunosuppressive therapy); 2) those without research authorization for use of medical records; 3) receipt of blood products or immunoglobulin within 3 months; 4) documented pneumococcal diseases (e.g., acute otitis media, acute sinusitis, community acquired pneumonia) with antibiotic treatment within one month prior to enrollment; and 5) non-Olmsted County, MN residents.

Measurement of serotype-specific anti-pneumococcal polysaccharide IgG

The details of measurement of pneumococcal antibodies were previously reported.¹⁴ Briefly, antibodies to 23 serotypes of *Streptococcus pneumoniae* which were measured by microsphere photometry method at the Mayo Clinic Clinical Immunology Lab.²⁴ A serotype-specific anti-pneumococcal polysaccharide antibody (IgG) concentration of 1.3 µg/mL or greater is considered an adequate or positive response.²⁵ The individual serotype-specific pneumococcal antibody concentrations were coded as a binary variable (0 vs. 1). For analysis, we summed the number of positive serotype-specific antibody levels (i.e., 0 vs. 1) and thus, the possible range of the number of positive serotype-specific antibody levels were 0–23.

Measurement of Serum 25 (OH)D

We measured serum 25(OH)D levels (ng/mL) at a single point in all subjects using mass spectrometry at Mayo Clinic.²⁶ 25(OH)D concentrations were log-transformed for data analysis because data for 25(OH)D levels did not follow the Gaussian distribution.

Measurement of IL-6, IL-13, and IFN-γ

We measured LPS (lipopolysaccharide) induced IL-6 (interleukin-6) secretion by PBMCs (mononuclear cells) and tetanus toxoid induced IL-13(interleukin-13) and IFN-γ (interferon-gamma) secretion by PBMCs. IL-6, IFN-γ and IL-13 secretion from PBMCs

cultured with LPS and tetanus toxoid for four days were measured by specific enzyme-linked immunosorbent assays (ELISA). The amount of IL-6, IL-13, and IFN- γ in culture supernatants was determined by ELISA using matched-pair antibodies (Pierce, Rockford, IL), according to the manufacturer's directions. The ELISA detection thresholds were as 0.5 pg/mL for IL-6, IL-13 and IFN- γ .

Ascertainment of asthma status

We enrolled only subjects who met the criteria for definite asthma in this study. Asthma status was ascertained by applying predetermined criteria used in previous studies.^{14, 20} Briefly, patients were considered to have definite asthma if a physician had made a diagnosis of asthma or if each of three conditions (1: specific asthma symptoms, 2: recurrence of asthma symptoms, and 3: two or more of eight specific asthma risk factors) were present. Patients were considered to have probable asthma if the first two of the above three conditions were present. We also confirmed asthma status at the time of enrollment.

Ascertainment of other atopic conditions

We determined atopic dermatitis or eczema and allergic rhinitis or hay fever based on a physician diagnosis documented in medical records. Also, we confirmed this diagnosis at the time of enrollment.

Determination of atopic sensitization status

Atopic sensitization status was defined in these analyses as a positive specific IgE response (> 0.35 kU/L) to at least one of the allergens tested (house dust mite, elm, oak, cat, ragweed, alternaria, and grass allergens). Allergen-specific IgE levels were determined in the Mayo Clinic Clinical lab, using the Phadia immunoCAP system (Phadia, Uppsala, Sweden).

Statistical analysis

We assessed the distribution of natural log-transformed serum 25(OH)D levels and positive serotype-specific pneumococcal antibody levels as both did not follow Gaussian. Subsequently, we characterized subjects with and without asthma with regard to pertinent variables. We used Pearson's correlation coefficient to assess the overall correlation between serum 25(OH)D levels and the number of positive serotype-specific pneumococcal antibody levels. To examine the potential effect modification by asthma, we determined the correlation between serum 25(OH)D levels and the number of positive serotype-specific pneumococcal antibody levels by asthma. We also assessed the potential effect modification of the correlation between serum 25(OH)D levels and the number of positive serotype-specific pneumococcal antibody levels by atopic dermatitis and/or allergic rhinitis and atopic sensitization status. Statistical significance was tested at a two-sided alpha error of 0.05, and data analysis was performed using Stata version 10 (State College, Texas)

RESULTS

Study subjects

The details of sociodemographic and clinical characteristics of study subjects are summarized in Table I. Briefly, of the 44 subjects, 23 (52.3%) were male, and 36 (81.8%) were Caucasians. Eight subjects (18.2%) were younger than 18 years of age. Twenty-one (48%) subjects had asthma, 20 (45%) had atopic dermatitis and/or allergic rhinitis, and 25(57%) had atopic sensitization status.

The association of 25(OH)D and pneumococcal antibody levels

Amongst all subjects, there was no significant correlation between serum 25(OH)D levels and the number of positive serotype specific pneumococcal antibody levels ($r = -0.14$, $p = 0.38$). However, stratified analysis results showed that there was a significant positive correlation between serum 25(OH)D levels and the number of positive serotype specific pneumococcal antibody levels in asthmatics, ($r = 0.45$, $p = 0.04$) whereas there was an inverse correlation in non-asthmatics ($r = -0.53$, $p = 0.01$) (Figure 1). There were similar trends for subjects with atopic sensitization status ($r = 0.27$, $p = 0.19$) and those without atopic sensitization status ($r = -0.41$, $p = 0.08$), but the correlations did not reach statistical significance (Figure 2). We also found that there were similar trends in subjects with atopic dermatitis and/or allergic rhinitis ($r = 0.58$, $p = 0.008$ for individuals with atopic dermatitis or allergic rhinitis vs. $r = -0.63$, $p = 0.001$ for those without such conditions) (Figure 3). As a secondary analysis, we analyzed the correlation between serum 25(OH)D levels and the number of positive serotype-specific pneumococcal antibody levels after stratifying pneumococcal vaccination status: vaccinated group, not-vaccinated group, and all subjects despite the limited statistical power (data not shown). Overall, we observed the similar effect modifying trends on the correlation between serum 25(OH)D and the number of positive serotype-specific pneumococcal antibody levels by atopic conditions. For example, among subjects without pneumococcal vaccinations ($n = 31$), there was a positive correlation trend between serum 25(OH)D levels and the number of positive serotype-specific pneumococcal antibody levels in asthmatics, ($r = 0.41$, $p = 0.17$), whereas there was an inverse correlation in non-asthmatics ($r = -0.46$, $p = 0.05$). Among those with pneumococcal vaccinations ($n = 13$), there was a similar positive correlation trend between serum 25(OH)D and the number of positive serotype-specific pneumococcal antibody levels in asthmatics, ($\rho = 0.68$, $p = 0.063$), whereas there was an inverse correlation in non-asthmatics ($\rho = -0.80$, $p = 0.10$).

The role of 25(OH)D in innate and cell-mediated immune functions

Overall, there was no correlation between serum 25(OH)D levels and IL-6 secretion by PBMCs stimulated with LPS (a measure of innate immune function). Also, we did not observe a significant correlation between 25(OH)D levels and IL-13 and IFN- γ secretion by PBMCs stimulated with tetanus toxoid (surrogate measures for cell-mediated immune function). These correlations were not significantly modified by asthma, atopic dermatitis and/or allergic rhinitis, and atopic sensitization status (data not shown).

DISCUSSION

In our study, asthmatics showed a positive correlation between serum 25(OH)D levels and the number of positive serotype-specific pneumococcal antibody levels, ($r = 0.45$, $p = 0.04$) but non-asthmatics showed an inverse correlation ($r = -0.53$, $p = 0.01$). These trends were stronger among those with and without atopic dermatitis and/or allergic rhinitis ($r = 0.58$, $p = 0.008$ vs. $r = -0.63$, $p = 0.001$, respectively). However, there were similar trends among those with and without atopic sensitization status but the correlation did not reach statistical significance. These results suggest that the association between serum 25(OH)D (an index of vitamin D status) and pneumococcal antibody response depends on the atopic status of individuals, and the relationship between serum 25(OH)D and pneumococcal antibody response may not be homogeneous for all individuals. The results based on the analysis stratified by pneumococcal vaccination status showed the similar trends (data not shown). Kriesel et al reported there were no significant differences in the overall influenza vaccine response between groups with and without 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) administration during influenza vaccination; however, they did not report the results stratified by atopic status.²⁷ Previous studies have reported the associations between 25(OH)D and respiratory infections and atopic diseases.^{17, 28–32} Ginde et al reported lower serum 25(OH)D levels were associated with a risk of recent upper respiratory infections (OR:1.24–1.36) and this association was stronger in individuals with asthma or chronic obstructive pulmonary disease (OR:2.26–5.67).³¹ There is a report suggesting that serum total IgG levels were negatively associated with serum 25(OH)D levels in certain individuals such as patients with cystic fibrosis.³³ At present, no studies similar to ours are available and there is scant information on the correlation between serum 25(OH)D and humoral immune function.^{34–36}

The results of previous studies on the relationship between 1,25(OH)₂D₃ and cytokine secretions reflecting innate and cellular immunities have been inconsistent.^{37, 38} The mechanisms by which 25(OH)D might influence pneumococcal antibody titers or humoral immune response in general are unknown. Further studies are needed to identify the mechanisms underlying our study findings. It is unknown whether this observation applies to humoral immune responses to other bacterial or viral antigens. Further investigations regarding the quantitative association between serum 25(OH)D and humoral responses are needed. Unlike humoral immune function such as pneumococcal antibody levels, IL-6, IL-13 and IFN- γ were not associated with serum 25(OH)D and there was no effect modification by atopic conditions (data not shown). The role of 25(OH)D in adaptive immunity needs further studies.

Although the mechanisms underlying our study findings are unknown, our study findings may have important public health implications for asthmatics given the concerns about *S. pneumoniae* as a significant public health threat, the knowledge that asthmatics are at a high-risk for invasive pneumococcal diseases,^{20, 39, 40} and that asthmatics often have suboptimal pneumococcal antibody levels.¹⁴ The role of nutritional intervention to improve pneumococcal antibody response in high-risk individuals for pneumococcal diseases such as those with atopic conditions may be considered.⁴¹ However, we caution that our results not be over-interpreted to mean that all subjects should receive vitamin D supplementation. The

recent Institute of Medicine report raised a concern over excessive vitamin D intake⁴² and medical community should remain vigilant about unrecognized harmful effects of certain treatments introduced in clinical medicine.⁴³ Previous studies have examined the association between 25(OH)D and innate immune function,^{6–8, 44, 45} but the results have been inconsistent.^{17–19, 46} Our study results suggest that the relationship between serum 25(OH)D levels and immune functions needs to be assessed in relation to atopic status, which may account for the potential inconsistency.

Our study has several potential limitations. Most asthmatics have other atopic conditions and atopic sensitization, and thus it is difficult to discern which specific condition is responsible for the relationship between 25(OH)D and pneumococcal antibody levels. Although this is a limitation, it could hint a potential causal attribute given the predictability and coherence. Our criteria for asthma and other atopic conditions were practical but might not be accurate. Given the lack of gold standard for defining asthma, misclassification of asthma ascertainment in our study is likely to allow null hypothesis to be supported. Another limitation of our study is limited statistical power, which did not allow analyses assessing complex interactions and adjustments. We did not collect dietary information regarding dietary vitamin D intake or sunlight exposure in this study. Finally, given the predominantly Caucasian population of our study, one needs to be cautious when generalize the findings to other racial groups.⁴⁷

In conclusion, 25(OH)D may enhance humoral immunity against *S. pneumoniae* in asthmatics but not in non-asthmatics. While individuals with atopic conditions may be encouraged to take vitamin D supplementation, the effect of vitamin D supplementation on immune functions in normal individuals needs to be assessed. A larger prospective study is needed to confirm our findings.

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Abbreviations used

SPD	Severe pneumococcal disease
DCs	Dendritic cells
Treg	Regulatory T cell
PBMCs	Mononuclear cells
IFN-γ	Interferon-gamma
LPS	lipopolysaccharide
IL-6	Interleukin-6

IL-13	Interleukin-13
ABPA	Allergic bronchopulmonary aspergillosis
25(OH)D	25-hydroxyvitamin D
1,25(OH)₂D₃	1,25-Dihydroxyvitamin D ₃

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Figure 1.

Association between serum 25-hydroxyvitamin D levels and the number of serotype positive pneumococcal antibodies in asthmatics and non-asthmatics. Y-axis: log-transformed number of serotype positive pneumococcal antibody levels (range: 1.79–3.14). X-axis: log-transformed 25-hydroxyvitamin D levels (range: 2.57–4.26). Data were fitted to a least square model. The correlation between serum 25-hydroxyvitamin D levels and the number of serotype positive pneumococcal antibody levels was modified by clinically defined asthma status.

Figure 2.

Association between serum 25-hydroxyvitamin D levels and the number of serotype positive pneumococcal antibody levels in participants with and without atopic sensitization status based on common allergen-specific IgE levels (< 0.35 IU/mL). Y-axis: log-transformed number of serotype positive pneumococcal antibody levels (range: 1.79–3.14). X-axis: log-transformed 25-hydroxyvitamin D levels (range: 2.57–4.26). Data were fitted to a least square model. The trend of correlation between serum 25-hydroxyvitamin D levels and the number of serotype positive pneumococcal antibody levels were similar in subjects classified by asthma.

Figure 3.

Association between serum 25-hydroxyvitamin D levels and the number of serotype positive pneumococcal antibody levels in subjects with and without other atopic conditions based on a physician diagnosis documented in a medical record (AD: atopic dermatitis and AR: allergic rhinitis). Y-axis: log-transformed number of serotype positive pneumococcal antibody levels (range: 1.79–3.14). X-axis: log-transformed 25-hydroxyvitamin D levels (range: 2.57–4.26). Data were fitted to a least square model. The correlation between serum 25-hydroxyvitamin D levels and the number of serotype positive pneumococcal antibody levels was modified by clinically defined AD and/or AR.

Table 1

Baseline characteristics of participants

Characteristic	Control (N=23)	Asthma (N=21)	p-value
Age at index date (y)			
Mean $\pm$ SD	39.9 $\pm$ 21.0	38.1 $\pm$ 18.6	0.77
Median (Interquartile range)	37.8 (59.6–24.8)	39.8 (23.5–54.5)	
Sex, no (%)			0.54
Male	11 (47.9)	12 (57.1)	
Female	12 (52.1)	9 (42.9)	
Tobacco smoke exposure at index date, no. (%)			0.50
Yes	1 (4.3)	2 (9.5)	
No	22 (95.7)	19 (90.5)	
Inhaled corticosteroid intake at the enrollment			0.41
Yes	0 (0.0)	11 (52.4)	
No	23 (100.0)	10 (47.6)	
Other atopic conditions (atopic dermatitis and/or allergic rhinitis)			<0.001
Yes	4 (17)	16 (76)	
No	19 (83)	5 (24)	
Atopic sensitization status *			< 0.001
Yes	7 (30.4)	18 (85.7)	
No	16 (69.6)	3 (14.3)	
Family history of asthma			0.001
Yes	4 (17.4)	13 (65.0)	
No	19 (82.6)	7 (35.0)	
Pneumococcal vaccinations			0.27
PCV-7	2 (8.7)	1 (4.7)	
PPV23	3 (13)	7 (33)	
Never received	18 (78.3)	13 (61.9)	
Comorbid conditions **			0.29
Yes	0 (0.0)	1 (4.8)	
No	23 (100.0)	20 (95.2)	
25-hydroxyvitamin D (ng/mL)			
Mean $\pm$ SD	35.6 $\pm$ 14.4	32.5 $\pm$ 11.6	0.44

* : 0.35 IU/mL specific IgE levels in house dust mite, elm, oak, cat, ragweed, alternaria, and grass allergens by using CAP;

** only one subject had the Advisory Committee on Immunization Practices (ACIP) recommended pneumococcal vaccine eligible conditions (chronic obstructive lung disease).