The Effect of Vitamin D Status on Pediatric Asthma at a University Hospital, Thailand

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INTRODUCTION

Asthma is a significant public health problem throughout the world; however, the prevalence of asthma varies widely between countries. The prevalence of asthma is higher in developed countries than in developing countries.1 In an International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence of asthma in Thai children increased from 12.2% in 1995 to 14.5% in 2001.2 The reason for different asthma prevalence in different parts of the world and its upward trend may be partly explained by gene and environment interactions. Vitamin D deficiency has recently been proposed as one of the factors associated with asthma epidemics.3 Vitamin D plays an important role in calcium and bone metabolism as well as immunomodulation. Many cells (brain, colon, prostate, breast, immune cells) contain vitamin D receptors and respond to 1,25-dihydroxyvitamin D (the active form of vitamin D).4 Recent studies in adults and children found a higher prevalence of hypovitaminosis D in asthmatics than in the normal population; in addition, low vitamin D levels are associated with a higher severity of asthma and impaired pulmonary function.5,6 Patients with vitamin D deficiency have shown to have increased airway hyper-responsiveness and increased corticosteroid requirements. Vitamin D might increase the response to glucocorticoid in asthmatic patients.7,8 In pregnancy, maternal vitamin D intake has an inverse correlation with risk of recurrent wheezing in childhood.9

The problems of vitamin D deficiency/insufficiency are in-
creasing throughout the world, especially in adolescents, young adults, and elderly populations. In Europe, 93%-97% of children in Denmark and Finland have a vitamin D level of less than 20 ng/mL (50 nmol/L). In Southeast Asia, 60%-63% of adults in Malaysia and Indonesia have a vitamin D level of less than 20 ng/mL. It was previously believed that hypovitaminosis D was not a problem in Thailand because Thailand is located near the equator and has abundant sunlight. However, current studies have shown that 77.8% of the premenopausal Thai women had a vitamin D level of less than 35 ng/mL. Vitamin D insufficiency (less than 30 ng/mL) was found in 69% of the Thai elderly population. Life-style modification and foods may be the causes of this problem; however, data on vitamin D levels in Thai children is limited.

In tropical countries, data on the effect of vitamin D status on asthma control is limited. Therefore, this study compared the vitamin D status between controlled, partly controlled, and uncontrolled asthmatic patients in the pediatric population and examine the correlation between vitamin D levels and pulmonary function/corticosteroid requirements.

**MATERIALS AND METHODS**

**Patients**

This cross-sectional study was conducted at the pediatric allergy clinic, Siriraj Hospital of Mahidol University (a tertiary care hospital). Thailand is located at the average latitude of 13° 45’ N which has a minute seasonal variation in the peak of sunlight. The Ethics Committee of Siriraj Hospital approved this study. Informed consent was given by each patient and parent.

Children who had a diagnosis of asthma confirmed by allergists and were aged between 6-18 years were enrolled between July 2011 and December 2012. We excluded patients who had underlying liver, kidney, or endocrine diseases that might affect vitamin D levels. Demographic data, dietary history, outdoor exercise (hours/week), adequacy of sun exposure (exposure to sun light more than 15 min/day and more than twice a week), clinical variable factors of asthma, and skin prick test (SPT) results were recorded. Dietary vitamin D was assessed by the intake of vitamin D-enriched foods, such as egg yolks, oily fish, and mushrooms (times/week). Patients who took vitamin D supplements were excluded. Participants’ history of asthma and the level of asthma control were assessed by Global Initiative for Asthma (GINA) guidelines.

Blood samples were obtained, and the plasma levels of calcium, phosphorus, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured by using a Modular P800 analyzer (Roche Diagnostics, Mannheim, Germany). The plasma levels of parathyroid hormone (PTH) and serum 25-hydroxy vitamin D were measured by electrochemiluminescence immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics) that measures both D2 and D3 derivatives of the 25-hydroxy vitamin D (25(OH)D) reported in nanograms per milliliter (ng/mL). Vitamin D levels were categorized into ‘insufficiency’ (levels between 20-30 ng/mL) and ‘deficiency’ (levels less than 20 ng/mL). Eosinophil counts were measured by using an UniCel DxH 800 analyzer (Beckman Coulter Inc., Brea, CA, USA).

**Skin prick test and pulmonary function test**

A skin prick test was done using common allergens: house dust mite (Dermatophagoides pteronyssinus and Dermatophagoides farinae), cockroach, animal dander (cat and dog), grass (Bermuda, Johnson), tree (Acacia), weed (careless weed), and mold (Alternaria, Curvularia, Cladosporium, Penicillium, and Aspergillus) manufactured by ALK, Port Washington, NY, USA. Histamine dihydrochloride (10 mg/mL) and 0.9% saline solution were used as positive and negative controls, respectively. The test was interpreted as positive if the mean wheal diameter (MWD) at 15 min was ≥ 3 mm when compared with the negative control. A pulmonary function test was performed by using a spirometer (nSpire Health, Inc., Longmont, CO, USA) in a KOKO model.

**Statistical Analyses**

All statistical analyses were performed with the SPSS package version 16 (SPSS Inc., Chicago, IL, USA). The demographic and clinical data of the patients were expressed using descriptive statistics (frequency, mean, median, SD, and range). Different characteristics between the 3 groups of the level of asthma control were assessed by the one-way analysis of variance (ANOVA) test (for parametric data), the Kruskal-Wallis test (for non-parametric data), and the chi-square test (for descriptive analysis). A P value of < 0.05 was considered statistically significant.

The degree of associations between vitamin D levels and pulmonary function as well as the doses of inhaled corticosteroids were estimated using partial linear correlations after adjustment for potential confounders (sex and age).

**RESULTS**

A total of 125 asthmatic patients with a mean ± SD age of 10.8 ± 3.0 years were enrolled in this study. There were 83 males (66.4%). The proportion of patients with different levels of asthma control according to the GINA classifications were 25.6% for uncontrolled patients, 36.8% for partly controlled patients, and 37.6% for controlled patients. Table 1 shows their major clinical and demographic characteristics.

We found fewer males in the uncontrolled and partly controlled groups than in the controlled group. Vitamin D deficiency occurred in 31.2% of uncontrolled asthmatic patients, which was a higher proportion than in partly controlled and controlled patients (17.4% and 12.8%, respectively); however, the difference was not statistically significant. The proportions of vitamin D
Table 1. Characteristics of uncontrolled, partly controlled, and controlled asthma

| Level of asthma control | Uncontrolled asthma (n = 32) | Partly controlled asthma (n = 46) | Controlled asthma (n = 47) | P value |
|-------------------------|-------------------------------|----------------------------------|---------------------------|---------|
| Age (months)            | 123.3 ± 35.0                 | 129.0 ± 34.5                    | 135.2 ± 36.6              | 0.339   |
| Sex (male)              | 18 (56.2%)                   | 26 (56.5%)                      | 39 (83%)                  | 0.010   |
| Vitamin D status        |                               |                                  |                           |         |
| Deficiency              | 10 (31.2%)                   | 8 (17.4%)                       | 6 (12.8%)                 | 0.114   |
| Insufficiency           | 12 (37%)                     | 19 (40.9%)                      | 24 (53.3%)                |         |
| Obesity                 | 7 (21.9%)                    | 16 (34.8%)                      | 17 (36.2%)                | 0.359   |
| Onset of asthma (months)| 24 (6-132)                   | 24 (4-148)                      | 24 (8-110)                | 0.922   |
| Comorbidities           |                               |                                  |                           |         |
| Allergic conjunctivitis| 29 (90.6%)                   | 45 (97.8%)                      | 45 (95.7%)                | 0.119   |
| Atopic dermatitis       | 4 (12.5%)                    | 4 (8.7%)                        | 2 (4.3%)                  | 0.405   |
| Food allergy            | 6 (18.8%)                    | 11 (23.9%)                      | 3 (6.4%)                  | 0.062   |
| Other comorbidity*      | 4 (12.5%)                    | 6 (13%)                         | 2 (4.3%)                  | 0.300   |
| Skin prick test Mites   | 27 (90%)                     | 39 (84.8%)                      | 33 (70.2%)                | 0.066   |
| Cockroaches             | 17 (56.7%)                   | 24 (52.2%)                      | 16 (34%)                  | 0.092   |
| Cat                     | 8 (26.7%)                    | 13 (28.3%)                      | 6 (12.8%)                 | 0.152   |
| Dog                     | 5 (12.9%)                    | 7 (15.9%)                       | 7 (15.9%)                 | 0.088   |
| Grasses                 | 11 (36.7%)                   | 12 (26.1%)                      | 8 (17%)                   | 0.151   |
| Tree                    | 3 (10%)                      | 9 (19.6%)                       | 1 (2.1%)                  | 0.024   |
| Molds                   | 7 (23.3%)                    | 5 (10.9%)                       | 7 (14.9%)                 | 0.337   |
| Pulmonary function test |                               |                                  |                           |         |
| FEV1                    | 87.8 ± 14.8                   | 85.9 ± 13.8                     | 89.1 ± 9.3                | 0.453   |
| FVC                     | 91.5 ± 15.6                   | 87.2 ± 13.7                     | 88.5 ± 8.9                | 0.495   |
| % changed FEV1          | 7.6 ± 6.6                     | 7.0 ± 7.3                       | 3.7 ± 4.0                 | 0.004   |
| FEV1/FVC                | 67.0 ± 13.7                   | 88.1 ± 7.6                      | 89.3 ± 7.5                | 0.463   |
| Eosinophil count (cell/mm³) | 355.1 (0-1,615)             | 419.8 (0-2,690)                 | 322 (115.1-1,035)         | 0.375   |
| Medications             |                               |                                  |                           |         |
| ICS                     | 7 (21.9%)                     | 18 (39.1%)                      | 20 (42.6%)                | 0.146   |
| LABA/ICS                | 11 (34.4%)                    | 20 (43.5%)                      | 15 (31.9%)                | 0.485   |
| LTRA                    | 2 (6.2%)                      | 7 (15.2%)                       | 3 (6.4%)                  | 0.266   |
| Immunotherapy           | 3 (9.4%)                      | 3 (6.5%)                        | 1 (2.1%)                  | 0.366   |
| Total dose of ICS (µg/day) | 200 (0-1,000)              | 320 (0-1,500)                   | 100 (0-500)               | 0.002   |
| Systemic steroid usage in previous month | 8 (25%) | 7 (15.2%) | 0 | 0.003 |
| Use SABA in previous month | 17 (53.1%) | 14 (30.4%) | 6 (12.8%) | 0.001 |
| Healthcare use          |                               |                                  |                           |         |
| Hospitalization (≥ 1/year) | 13 (40.6%)                | 12 (26.1%)                      | 0                         | <0.001  |
| ER visit 1-3 times/year | 23 (71.9%)                   | 32 (69.6%)                      | 0                         | <0.001  |
| 3 times/year            | 6 (18.8%)                    | 5 (10.9%)                       | 0                         | <0.001  |
| Family history of asthma| 11 (34.4%)                   | 14 (30.4%)                      | 12 (25.5%)                | 0.691   |
| Environment             |                               |                                  |                           |         |
| Household pets           | 12 (37.5%)                   | 24 (52.2%)                      | 14 (29.8%)                | 0.083   |
| Passive smoking         | 13 (40.6%)                   | 18 (39.1%)                      | 18 (38.3%)                | 0.979   |
| Income (Baht/month)     | 20,000                       | 20,500                          | 20,000                    | 0.650   |
| (6,000-100,000)         | (5,000-100,000)              | (3,500-100,000)                 |                           |         |

*Other comorbidities, such as sinusitis, obstructive sleep apnea and gastroesophageal reflux disease.

ED, emergency department; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; percentage (%) changed FEV₁, percent change in FEV₁ after receiving short acting β₂ agonist; FEV₁/FVC, ratio between forced expiratory volume in 1 sec and forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β₂ agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β₂ agonist.
insufficiency were not statistically different between the 3 groups. Short-acting β2 agonists (SABAs) and systemic corticosteroids were used more often in the uncontrolled group than in the other groups \((P<0.05)\). The uncontrolled and partly controlled groups also used higher doses of inhaled corticosteroids (ICSs), with more ED visits and hospitalizations, than the controlled group \((P<0.05)\). There was no significant difference between the 3 groups in pulmonary function; however, uncontrolled and partly controlled groups had a higher percent \((%)\) change of forced expiratory volume in 1 second \((FEV1)\) after they received the bronchodilator than the controlled group.

The proportions of obesity \((\text{weight for height, higher than 120%})\), the onset of asthma, eosinophil counts, a family history of asthma, household income, and environmental factors were not significantly different between the 3 groups. Most of the patients had allergic rhinoconjunctivitis \((95.2\%)\) as a comorbidity and house dust mite sensitization \((80.5\%)\). There were 7 patients \((5.6\%)\) who had received subcutaneous immunotherapy.

The mean serum vitamin D levels of the uncontrolled, partly controlled, and controlled groups were 25.9 ± 8.6, 32.9 ± 8.0 ng/mL, respectively (Fig. 1). There were no significant differences between the 3 groups. Fig. 2 shows the distribution of serum vitamin D levels in asthmatic patients. The plasma levels of calcium, phosphorus, creatinine, AST, and ALT were within the normal range.

There were 24 children \((19.2\%)\) with vitamin D deficiency, 56 children \((44.8\%)\) with vitamin D insufficiency, and 45 children \((36\%)\) with vitamin D sufficiency \((Table\ 2)\). The vitamin D deficiency patients were older and had a significantly more delayed onset of asthma and higher PTH levels than the vitamin D insufficiency and sufficiency patients. There were no significant differences in sex, obesity, skin test reactivity, eosinophil counts, reliever use, a history of ED visits and hospitalizations for asthma in the previous year between different vitamin D statuses.

The medications used, such as ICSs, long-acting β2 agonists \((LABAs)/ICSs,\) leukotriene receptor antagonists \((LTRAs),\) systemic steroids, and immunotherapy were not significantly different between different vitamin D statuses. There were no significant differences in household income, a history of vitamin D-enriched food \((\text{egg yolks, oily fish, and mushrooms})\) intake, and adequate sun exposure \((\text{exposure to sun light more than 15 min/day and more than 2 times a week})\) between the vitamin D deficiency, insufficiency, and sufficiency patients. The vitamin D deficiency patients spent fewer hours of outdoor exercise than the vitamin D insufficiency and sufficiency patients \((but\ this\ was\ not\ statistically\ significant)\). After adjustments for sex and age, there were no significant correlations between serum vitamin D and FEV1 \((\text{partial } r=0.09, P=0.339)\), FVC \((\text{partial } r=-0.007, P=0.944)\), percent \((%)\) changed FEV1 \((\text{partial } r=-0.082, P=0.384)\), FEV1/FVC \((\text{partial } r=0.124, P=0.190)\), and the doses of ICSs \((\text{partial } r=0.126, P=0.165)\).

**DISCUSSION**

Our study classified the level of asthma control based on the GINA guideline.\(^1\) The percentage of reliever use, hospitalization, ED visits, systemic corticosteroid usage, and percent \((%)\) change in FEV1 were significantly higher in the uncontrolled group than in the partly controlled and controlled groups. This confirms that our patients were properly classified.

In this study, 64% of the asthmatic children had vitamin D deficiency/insufficiency. This is almost the same as the prevalences in pre-menopausal and elderly women reported by previous Thai population studies.\(^14\,15\) The parathyroid levels were higher in the vitamin D deficiency patients than in the insufficiency and sufficiency patients. This supports the compensatory mechanism of the body for maintaining the normal calcium level. Taken together, it is implied that vitamin D deficiency and insufficiency are serious problems in Thailand as well as in other countries located in abundant sun-exposure areas.\(^18\) This may be due to behavioral factors, such as sunscreen use, de-
increased time-spent outdoors, and lower vitamin D input from diets. However, in our study, we could not predict vitamin D statuses using questions about sun exposure or vitamin D-enriched food intake. A well-designed questionnaire with a larger sample size will be needed to find the correlation between vitamin D levels and sun exposure/vitamin D-enriched food intake.

In this study, there were no significant differences in serum vitamin D levels between the levels of asthma control, which is inconsistent with the results of previous studies. Gupta et al. reported that children with severe refractory asthma were found to have lower vitamin D levels than those with moderately controlled or controlled asthma. 

Chinellato et al. investigated the correlation of serum vitamin D levels and asthma control and found a weak correlation between serum vitamin D levels and the control of asthma symptoms. However, some studies reported that low vitamin D levels are associated with an increased bronchodilator response, pulmonary function, hospitalization, ED visits, the use of anti-inflammatory medications, and ICS doses. Searing et al. demonstrated that serum vitamin D levels inversely correlate with 

| Table 2. Investigated parameters according to vitamin D status |
|---------------------------------------------------------------|
| **Vitamin D status** | **Deficiency (n=24)** | **Insufficiency (n=56)** | **Sufficiency (n=45)** | **P value** |
| Age (months) | 145±32.2 | 133.5±35.8 | 117.1±32.9 | 0.003 |
| Sex (male) | 13 (54.2%) | 40 (71.4%) | 30 (66.4%) | 0.325 |
| Obesity | 7 (29.2%) | 23 (41.1%) | 10 (22.2%) | 0.123 |
| Onset of asthma (months) | 48 (7-148) | 24 (6-144) | 24 (4-110) | 0.034 |
| Skin prick test | | | | |
| Mite | 22 (95.7%) | 44 (78.6%) | 33 (75%) | 0.114 |
| Cockroach | 10 (43.5%) | 26 (46.4%) | 21 (47.7%) | 0.945 |
| Eosinophil count (median, cell/mm³) | 391.4 (38.6-1,690.9) | 400.2 (0-1,671.8) | 356.6 (112.7-1,615.3) | 0.991 |
| Parathyroid hormone (pg/mL) | 55.9 (33.9-92.0) | 51 (21.5-170.1) | 41.9 (15.3-131.3) | 0.002 |
| Medications | | | | |
| ICS | 8 (33.3%) | 21 (37.5%) | 16 (35.6%) | 0.936 |
| LABA/ICS | 7 (29.2%) | 23 (41.1%) | 17 (37.8%) | 0.602 |
| LTRA | 3 (12.5%) | 4 (7.1%) | 5 (11.1%) | 0.691 |
| Immunotherapy | 3 (12.5%) | 2 (3.6%) | 2 (4.4%) | 0.258 |
| Total dose of ICS (µg/day) | 180 (0-500) | 200 (0-1,500) | 200 (0-1,000) | 0.481 |
| Receive systemic steroid in previous month | 4 (16.7%) | 3 (5.4%) | 8 (17.8%) | 0.141 |
| Use SABA in previous month | 8 (33.3%) | 17 (30.4%) | 12 (29.6%) | 0.835 |
| Health care use in previous year | | | | |
| Hospitalizations | 5 (20.8%) | 8 (14.3%) | 12 (26.6%) | 0.494 |
| ER visit | 16 (66.7%) | 26 (46.4%) | 24 (53.3%) | 0.250 |
| Outdoor exercise (hours/week) | 2 (0-7) | 2.3 (0-14) | 3.5 (0-7) | 0.304 |
| Adequate sun exposure | 13 (54.2%) | 24 (42.9%) | 29 (64.4%) | 0.094 |
| Enriched vitamin D containing food* (times/week) | 3.8 (0.5-8) | 4.8 (0-9) | 3.5 (0-10.5) | 0.83 |
| Income (Baht/month) | 20,000 (5,000-100,000) | 21,000 (3,500-100,000) | 20,000 (4,000-90,000) | 0.303 |

ED, emergency department; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β2 agonist.

We also could not find the correlation between serum vitamin D levels and pulmonary function. This is supported by the study of Devereux et al. which showed no association between vitamin D levels and asthma severity/pulmonary function. Chinellato et al. found a weak correlation between serum vitamin D levels and FVC but no correlations between serum vitamin D levels and other parameters of lung function—total IgE, eosinophil counts, or the size of skin prick test. However, some studies reported that low vitamin D levels are associated with an increased bronchodilator response, pulmonary function, hospitalization, ED visits, the use of anti-inflammatory medications, and ICS doses. Searing et al. demonstrated that serum vitamin D levels inversely correlate with FEV1, FVC, the number of positive SPT, the use of ICSs, the use of oral steroids, total steroid dose and the use of LABAs. They also stated that vitamin D enhances glucocorticoid action in vitro. In our study, serum vitamin D levels did not correlate with SPT, the use of ICSs, total doses of ICSs, the use of LABAs and eosinog-
phils counts.

The possible explanation for no association of vitamin D status with the levels of asthma control or pulmonary function may be that this is a cross-sectional study. Long-term follow-up studies focusing on changes in vitamin D status and asthma parameters will be needed to clarify the effect of vitamin D status on asthma. Furthermore, many confounding factors can affect vitamin D levels or asthma severity. The association between serum vitamin D and asthma severity may depend on the genotype or phenotype of asthmatic patients.

In conclusion, there was no significant correlation between serum vitamin D levels and asthma control statuses in Thai asthmatic children. More studies are required to determine the role of vitamin D in asthma and the promising role of vitamin D supplements in such patients.

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