APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Effect of vitamin D on lung function assessed by forced oscillation technique in asthmatic children with vitamin D deficiency: A randomized double-blind placebo-controlled trial

Napatsayod Swangtrakul, Wiparat Manuyakorn, Pat Mahachoklertwattana, Potjanee Kiewngam, Cherapat Sasisakulporn, Wanlapa Jotikasthira, Wasu Kamchaisatian, Suwat Benjaponpitak

Abstract

Background: The role of vitamin D and asthma in pulmonary function changes showed conflicting result.

Objective: To evaluate if vitamin D treatment would improve lung function assessed by forced oscillation technique (FOT) in vitamin D deficient asthmatic children.

Methods: A randomized double-blind placebo-controlled trial was performed in children, aged 3-18 years with well controlled asthma. Serum total 25(OH)D and FOT parameters including respiratory resistance at 5 Hz (R5), at 20 Hz (R20), respiratory reactance at 5 Hz (X5) and area of reactance (ALX), resonance frequency (Fres) were evaluated at baseline, 1 month and 3 months. Vitamin D deficient patients (serum total 25(OH)D < 20 ng/ml) were randomized to receive treatment with vitamin D2 (tVDD) or placebo (pVDD). Non-vitamin D deficient patients (nVDD) received placebo as a control group.

Results: A total of 84 children were recruited, 43 patients in nVDD group, 20 in tVDD group and 21 in pVDD group. There were no significant differences in age, sex, height and weight among groups. There were no significant differences of FOT parameters among groups at all visits. There was a trend toward decrease in R5/R20 from baseline to 1 month and 3 months visit in all groups, but the statistically significant improvement was observed only in nVDD group. Serum 25(OH)D showed no correlation with % predicted of FOT measures.

Conclusion: Vitamin D treatment in asthmatic children who had vitamin D deficiency may have no short term beneficial effect on pulmonary function assessed by FOT. Vitamin D supplementation in all asthmatic patient needs further study.

From:
Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Corresponding author:
Wiparat Manuyakorn
Division of Pediatrics Allergy and Immunology,
Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital,
Mahidol University Rama VI Rd, Ratchathewi, Bangkok 10400, Thailand
E-mail: mwiparat@hotmail.com

Introduction

Asthmatic patients who have low serum 25(OH)D have been shown to have airway hyperresponsiveness, impaired lung function, increased exacerbation and reduced corticosteroid responsiveness.[1-3] Nonetheless, the effect of vitamin D supplement in asthma patients showed inconsistent results. Some studies reported no beneficial effect of vitamin D supplement on level of asthma control and changes in spirometer parameters.[4,5] A recent meta-analysis has demonstrated that vitamin D supplementation in mild to moderate asthma protected against severe asthma attacks.[6] A cross-sectional study in Thai asthmatic children reported no significant correlations between serum vitamin D and spirometer parameters.[7] The possible explanation for the inconsistent association of vitamin D status with pulmonary function may be that the assessment with spirometry was not sensitive enough to measure small airway change in asthma.[8] Recently, the Forced Oscillation Technique

(FOT) has been introduced, it is a simple, noninvasive technique performed during tidal breathing that is easy to apply and less cooperate with the patient. FOT measures the respiratory system resistance and lung reactance.[9] FOT measurement was suggested to be more sensitive than spirometry in detecting subtle changes of lung function in children.[10] This study was aimed to evaluate changes in FOT parameters after vitamin D treatment in vitamin D deficiency asthmatic children compared with placebo.

Methods

Participants

Eligible participants were asthmatic children aged 3-18 years who had controlled asthma according to GINA guideline for a least 1 month. Diagnosis of asthma was made based on GINA 2016. Exclusion criteria included: chronic diseases, e.g. chronic renal failure, chronic liver disease, chronic respiratory disease; malabsorption; having lower respiratory tract infection within 4 weeks; oral medications interfering with vitamin D metabolism; or serum total 25(OH)D less than 10 ng/ml.

Study Design and Treatment

The study was a randomized, double-masked, parallel group trial (**Figure 1**) from March 2017 through March 2018. Children who met the inclusion criteria were collected demographic data, complete blood count, serum total 25(OH)D, skin prick test, and FOT parameters at baseline. Patients with vitamin D deficiency (VDD) defined as serum total 25(OH)D < 20 ng/ml were randomly assigned to either placebo or vitamin D2 (the British Dispensary (L.P.) Co., Ltd., Bangkok,

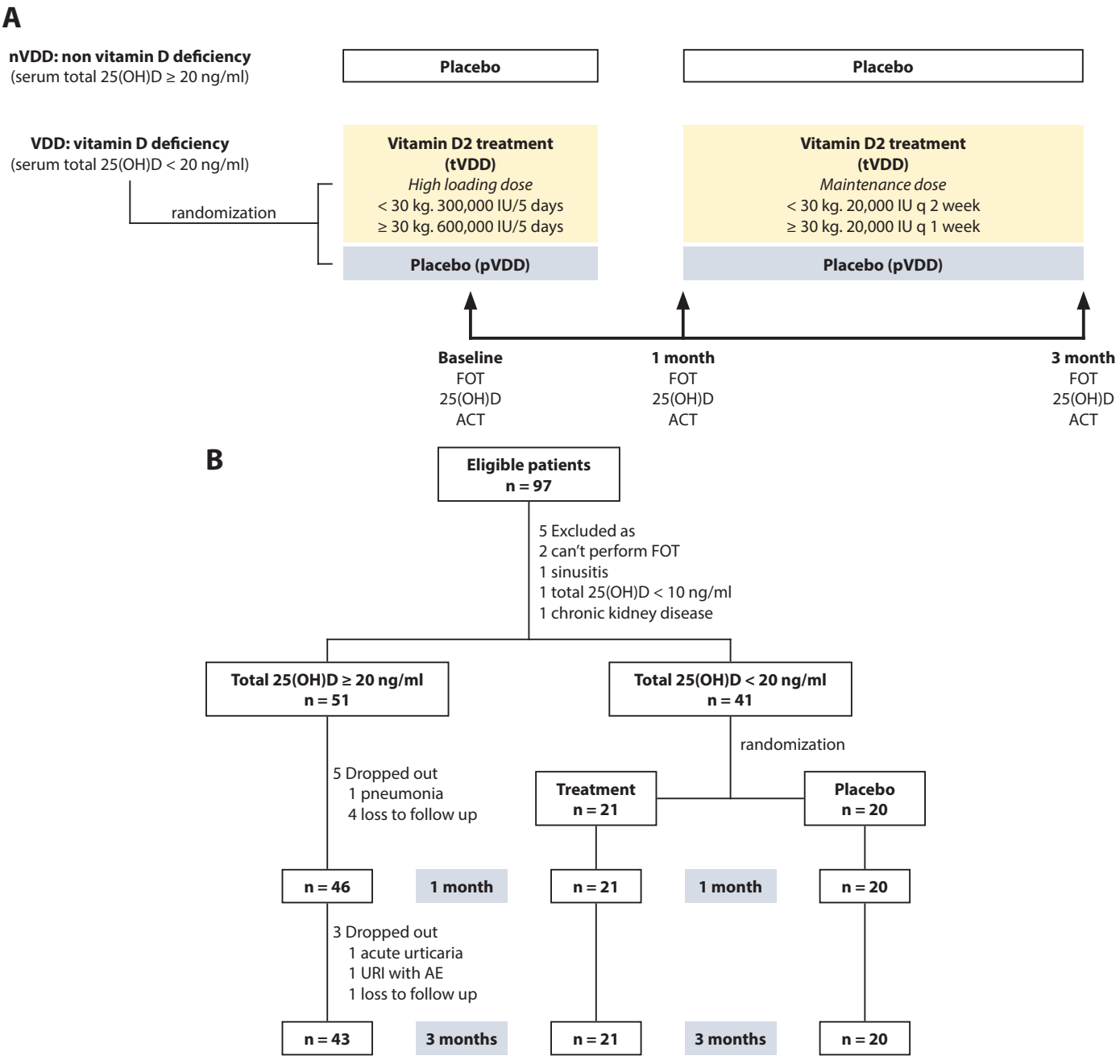

Figure 1. Study protocol (A) and participant flow of enrolled children (B).

Thailand) as follow: body weight < 30 kg.: vitamin D2 300,000 IU divided in 5 days in the first visit then a maintenance dose of 20,000 IU every 2 weeks started at 1-month visit, body weight ≥ 30 kg: vitamin D2 600,000 IU divided in 5 days in the first visit then a maintenance dose of 20,000 IU every week started at 1-month visit. Children who had non-vitamin D deficiency (nVDD) patients defined as the serum total 25(OH)D ≥ 20 ng/ml received placebo as the control group. The definition of vitamin D deficiency (VDD) was based on Endocrine Society Practice Guideline on Vitamin D.[11] The placebo vitamin D soft gelatin capsules matched in appearance those containing vitamin D2 were obtained from the British Dispensary (L.P.) Co., Ltd, Bangkok, Thailand. Randomization was done using the box of four. Blinding was done by putting the code for each group. All investigators except for one research nurse (WJ) were blinded to the patient's vitamin D status and randomization. WJ was responsible for dispending vitamin D2 or placebo to the patients. FOT parameters and level of asthma control were recorded at baseline, 1-month and 3-month visit. Study protocol was shown in **Figure 1A**. The study was approved by the institutional ethics committee (Protocol number ID 01-60-09). Written informed consent was obtained from parents and children. This clinical trial was registered at Thai Clinical Trials Registry (No. TCTR20170422001).

Level of asthma control

Level of asthma control was evaluated by pediatric asthma control test (P-ACT) for patients aged 4–11 years[12] or the asthma control test (ACT) for patients aged 12– 15 years. P-ACT/ACT score ≥ 20 was defined as well controlled.[13,14]

Forced Oscillation Technique Measurement

Forced Oscillation Technique was performed using MostGraph-02 (Chest M.I., Co Ltd, Tokyo, Japan). Children were asked to breathe through a mouthpiece that incorporated to a bacterial filter. The regular tidal breathing was performed with a nose-clip while the technician supported the cheeks and lower jaw. During the measurement, the flow signal was monitored for the signs of glottis closure and air leakage. FOT was performed during spontaneous tidal breathing. During data acquisition, pressure and flow traces were graphically displayed in real time. The measurements began automatically after two consecutive stable respirations; for this instrument, two consecutive and consistent respiratory signals that measure a coherence of 0.7 or higher were required for the initiation of the measurements. In addition, the operator evaluated the graphical measurement of respiratory resistance in real time during the examination. If the operator observed an apparent irregularity in the signal images, the subject was re-examined until a successful examination was achieved. Measurements were accepted when the tracings showed uninterrupted breathing during data acquisition. Measurements were rejected if disturbed by coughing, breath holding, swallowing or vocalization. The measurements were considered acceptable only when the time segment chosen for analysis lasted for at least 20 seconds. FOT parameters including respiratory resistance at 5 Hz (R5), respiratory resistance at 20 Hz (R20), and respiratory reactance at 5 Hz (X5), area of reactance (ALX), resonance frequency (Fres) and the percentage of the predicted (% predicted) of FOT values were recorded. Pre- and post-bronchodilator with 400 mcg of salbutamol inhalation were evaluated. Percentage of bronchodilator response (% BDR) was calculated from the difference absolute value obtained before and after salbutamol inhalation then divided by the absolute values before salbutamol inhalation and the result was multiplied by 100.

Serum total 25(OH)D

Fasting blood sample for serum total 25(OH) vitamin D levels blood samples were obtained during 6-8 am. Serum concentrations of 25(OH)D was analyzed by using a chemiluminescence immunoassay (LIASON® XL).

Statistical methods

Analysis was performed on all of the randomized patients who had both baseline and follow-up data and had continued the study medication. Since there is no previous report on the changes of FOT measures after treatment with vitamin D in asthmatic patients. The sample size was calculated from previous study on the effect of Vitamin D supplementation in asthma by assessing ATAQ score.[15] A sample size of 18 patients (the treatment arm) was expected to have a 90% power and a 2-sided alpha error of 0.01. Analysis was performed in patients who had completed 3 visits data. The changes in FOT parameter were analyzed using repeated-measures analysis of covariance models. Differences among groups in each visit were analyzed using analysis of covariance for continuous data and chi square test for categorical data. Data were analyzed by SPSS Ver 18.0. Statistical significance was considered at p value < 0.05.

Results

A total of 97 participants who met the inclusion criteria were screened, 5 patients were excluded due to the diagnosis of sinusitis, chronic kidney disease, serum total 25(OH)D < 10 ng/ml and FOT could not be performed in 2 patients. Ninety two asthmatic children were recruited: 41 children (44.6%) had total 25(OH)D < 20 ng/ml (VDD) and 51 children had total 25(OH)D ≥ 20 ng/ml (nVDD): 40 children (43.5%) had total 25(OH)D 21-30 ng/ml and 11 children (12%) had total 25(OH)D > 30 ng/ml. Forty one children in VDD group were randomized: 21 children in VDD group with treatment (tVDD), and 20 children in VDD group with placebo (pVDD). Eight patients (15.6%) in nVDD group were dropped out. As a result a total of 84 asthmatic children were analyzed (**Figure 1B**).

Baseline Characteristics of the study participants

The mean (SD) age of the asthmatic patients was 9.99 (3.10) years and 57.1% of patients were male. The mean serum total 25(OH)D was 21.58 ± 6.31 ng/ml. There were no significant differences of age distribution, height, weight, body mass index, aeroallergen sensitization, blood eosinophil count, atopy, dosage of inhaled corticosteroid used and asthma control test score among nVDD, tVDD and pVDD. Baseline FOT parameter values, % predicted of FOT values, and % BDR were no significant differences among groups except for the value of R20. However, post hoc analysis using a Bonferroni correction

applied to the significance criterion showed no significant difference in baseline R20 (**Table 1**).

Comparison of FOT parameters at 1, 3 months among groups

The mean (SD) total serum total 25(OH)D in nVDD, tVDD and pVDD were 25.65 (5.48), 48.26 (14.71) and 17.52 (3.77) ng/ml at 1 month and 25.01 (5.52), 30.05 (9.37) and 19.53 (5.57) ng/ml at 3 month, respectively (**Figure 2**). There were no significant differences in FOT parameter values, % predicted and % BDR among groups at 1 month and 3 months (**Table 2**).

Changes in FOT parameters among visits in nVDD, tVDD and pVDD

The decrease of FOT parameters was observed in all groups but the significant changes of R5 and R20 were demonstrated only in nVDD and pVDD groups (**Table 3**). The percentage

Table 1. Baseline characteristics of the participants

Parameters	nVDD group n = 43	Vitamin D deficiency patients		P-value
		tVDD n = 21	pVDD n = 20	
Total 25(OH)D level (ng/ml)	26.6 (4.6)	16.5 (2.2)	16.2 (2.3)	< 0.001
Gender: male	28 (58.3)	11 (52.3)	9 (45)	0.28
Height (cm.)	135.3 (18.0)	140.8 (16.1)	145.8 (17.3)	0.08
Weight (kg.)	35.3 (15.6)	39.5 (13.7)	44.0 (16.5)	0.11
BMI (kg/m^2)	18.3 (4.1)	19.5 (3.8)	20.0 (4.9)	0.31
Aeroallergen sensitization	29 (67.4)	16 (80)	13 (65)	0.51
Blood eosinophil (cu.mm.)	350 (156-532)	414.10 (191-635)	274 (137-588)	0.70
AEC ≥ 300 cell/μL	25 (58.1)	12 (57.1)	10 (50)	0.82
Atopy, no (%)				
- food allergy	9 (20.9)	5 (23.8)	3 (15)	0.77
- atopic dermatitis	10 (23.3)	7 (33.3)	2 (10)	0.20
- allergic rhinitis	40 (93.0)	20 (95.2)	18 (90)	0.80
Dosage of inhale corticosteroid*				0.24
- low dose	28 (65.1)	14 (66.7)	15 (75)	
- medium dose	8 (18.6)	2 (9.5)	0	
- high dose	0	0	1 (5)	
ACT/P-ACT ≥ 20	41 (95.3)	20 (95.2)	18 (90)	0.68
FOT parameters				
R5 (cmH_2O/L/S) % predicted R5	8.1 (3.3) 104.2 (33.2)	6.5 (2.7) 91.5 (25.7)	6.7 (2.8) 104.8 (31.7)	0.08 0.22
R20 (cmH_2O/L/S) % predicted R20	7.1 (2.4) 131.7 (33.6)	5.8 (1.9) 116.8 (31.0)	5.9 (2.0) 125.9 (29.7)	0.05 0.09
X5 (cmH_2O/L/S) % predicted X5	-1.3 (-2.5 to -0.6) 48.4 (24.5-48.4)	-0.9 (-1.1 to -0.4) 33.7 (26.8-61.0)	-0.8 (-1.4 to -0.5) 37.6 (23.5-56.6)	0.13 0.21
R5-R20 (cmH_2O/L/S)	0.89 (0.13-1.51)	0.40 (0.07-1.17)	0.465 (0.21-1.22)	0.15
ALX (cmH_2O/L)	6.77 (2.22-18.1)	3.64 (1.41-7.49)	2.88 (1.66-7.71)	0.16
Fres (Hz)	11.96 (8.46-16.88)	9.62 (7.17-12.80)	9.26 (8.08-2.95)	0.24
% BDR of R5	21.8 (12.2-37.6)	19 (14.7-24.4)	24.8 (14.1-32.3)	0.59
% BDR of R20	20.9 (14.2-32.1)	17.1 (10.1-24)	21.3 (15.4-30.7)	0.38
% BDR of ALX	47.5 (31.32-71.4)	38.9 (23.66-68.55)	47.9 (38.87-73.55)	0.18

Data presents as N (%), mean (sd) or median (IQR) *according to GINA guideline 2016, [a] difference from nVDD group,
nVDD = non-vitamin D deficiency, tVDD = vitamin D deficiency with treatment, pVDD = vitamin D deficiency with placebo, AEC = absolute eosinophil count, ACT = asthma control test, P-ACT = pediatric asthma control test, R5 = resistance at 5 Hz, R20 = resistance at 20 Hz, X5 = reactance at 5 Hz, ALX = area of reactance, Fres = resonance frequency and BDR = bronchodilator response

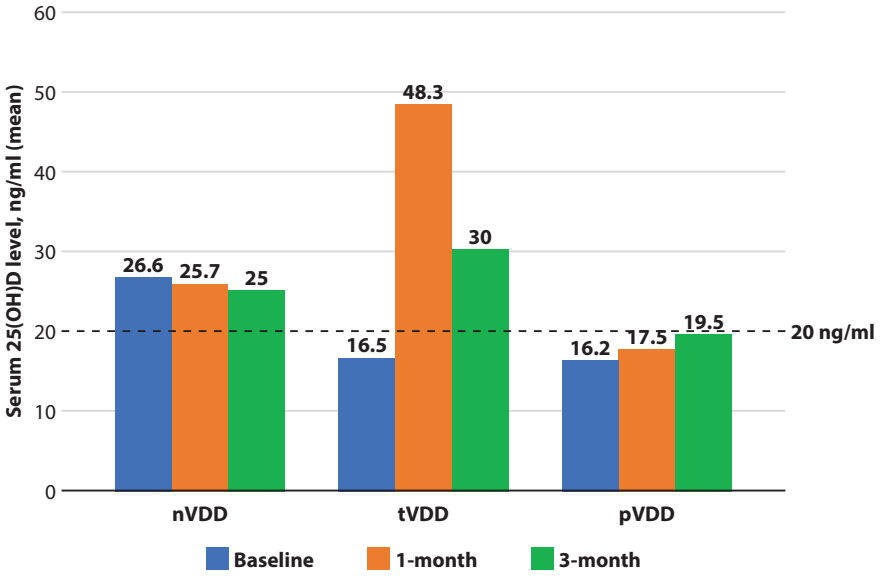

Figure 2. Level of vitamin D at baseline, 1 month and 3 months visit.

Table 2. Comparison of FOT parameters at 1 and 3-month follow up among groups

Parameters	nVDD n = 43	tVDD n = 21	pVDD n = 20	P-value
1 month				
• R5 ($cmH_2O/L/S$)	7.7 (3.4)	6.1 (2.2)	6.0 (2.4)	0.05
• % predicted R5	98.3 (33.1)	87.8 (17.9)	93.8 (22.2)	0.36
• R20 ($cmH_2O/L/S$)	6.7 (2.3)	5.5 (1.5)	5.5 (1.8)	0.98
• % predicted R20	124.1 (31.3)	110.7 (20.4)	116.7 (22.3)	0.16
• X5 ($cmH_2O/L/S$)	-1.2 (-1.8 to -0.5)	-0.7 (-1.5 to -0.3)	-0.7 (-1.3 to -0.5)	0.64
• % predicted X5	42.6 (27.4-58.0)	33.1 (23.6-58.9)	39.3 (22.7-64.5)	0.44
• R5-R20 ($cmH_2O/L/S$)	1.01 (0.16-1.55)	0.37 (0.1-1.29)	0.46 (-0.13 to1.14)	0.37
• ALX (cmH_2O/L)	5.41 (1.77-11.29)	2.69 (1.14-8.67)	3.27 (2.01-7.07)	0.18
• Fres(Hz)	11.69 (8.35-15.84)	9.05 (7.10-14.04)	9.29 (7.86-12.89)	0.27
• % BDR of R5	23.7 (15.3-35.9)	22.5 (9.6-29.3)	24.2 (15.4-29.6)	0.27
• %BDR of R20	23.2 (15.9-31.7)	17.8 (6.4-24.2)	18.9 (11.7-25.1)	0.56
• % BDR of ALX	49.5 (29.9-58.4)	43.05 (32.35-60.77)	54.3 (26.15-65.6)	0.84
3 months				
• R5 ($cmH_2O/L/S$)	7.1 (2.8)	6.2 (2.4)	6.1 (3.0)	0.89
• % predicted R5	94.3 (25.4)	89.8 (20.5)	92.4 (19.6)	0.76
• R20 ($cmH_2O/L/S$)	6.2 (1.9)	5.6 (1.7)	5.5 (2.1)	0.88
• % predicted R20	117.7 (24.2)	112.9 (23.3)	114.2 (21.6)	0.70
• X5 ($cmH_2O/L/S$)	-1.2 (-1.5 to -0.6)	-0.6 (-1.3 to -0.4)	-0.9 (-1.2 to -0.4)	0.60
• % predicted X5	36.2 (25.1-52.7)	28.4 (24.1-48.7)	41.5 (33.7-48.8)	0.39
• R5-R20 ($cmH_2O/L/S$)	0.89 (0.12-1.41)	0.5 (0.22-1.08)	0.48 (-0.1 to 0.77)	0.31
• ALX (cmH_2O/L)	5.37 (2.14-10.33)	2.22 (1.37-6.46)	4.22 (1.62-5.5)	0.18

Data presents as N (%), mean (sd) or median (IQR). nVDD = non-vitamin D deficiency, tVDD = vitamin D deficiency with treatment, pVDD = vitamin D deficiency with placebo, R5 = resistance at 5 Hz, R20 = resistance at 20 Hz, X5 = reactance at 5 Hz, ALX = area of reactance, Fres = resonance frequency and BDR = bronchodilator response

Table 2. (Continued)

Parameters	nVDD n = 43	tVDD n = 21	pVDD n = 20	P-value
3 months (Continued)				
• Fres (Hz)	11.3 (8.5-14.86)	8.1 (7.26-12.68)	10.24 (7.93-11.78)	0.12
• % BDR of R5	23.4 (19.3-28.5)	21.1 (10.6-28.8)	24.9 (16.2-35.2)	0.14
• % BDR of R20	12.9 (20.1-27.3)	15.9 (11.5-28.3)	19.8 (15.9-27.1)	0.34
• %BDR of ALX	49.9 (29.2-66.2)	31.3 (15.05-55.45)	40.4 (24.4-53.85)	0.15

Data presents as N (%), mean (sd) or median (IQR). nVDD = non-vitamin D deficiency, tVDD = vitamin D deficiency with treatment, pVDD = vitamin D deficiency with placebo, R5 = resistance at 5 Hz, R20 = resistance at 20 Hz, X5 = reactance at 5 Hz, ALX = area of reactance, Fres = resonance frequency and BDR = bronchodilator response

Table 3. Comparison of FOT parameters at 1 month and 3 months from baseline in each group

nVDD	Baseline	1 month	*P value	3 month	#P value
R5 ($cmH_2O/L/S$)	8.1 (3.4)	7.7 (3.4)	0.07	7.1 (2.8)	0.001
R20 ($cmH_2O/L/S$)	7.1 (2.5)	6.7 (2.3)	0.01	6.18 (1.93)	< 0.001
X5 ($cmH_2O/L/S$)	-1.3 (-2.5 to -0.6)	-1.2 (-1.8 to -0.5)	0.01	-1.2 (-1.5 to -0.6)	0.004
R5-R20 ($cmH_2O/L/S$)	0.89 (0.13-1.51)	1.01 (0.16-1.55)	0.65	0.89 (0.12-1.41)	0.79
ALX (cmH_2O/L)	6.77 (2.22-18.1)	5.41 (1.77-11.29)	0.04	5.37 (2.14-10.33)	0.07
Fres (Hz)	11.96 (8.46-16.88)	11.69 (8.35-15.84)	0.08	10.24 (7.93-11.78)	0.62
% BDR R5	23.6 (12.6-38.4)	23.70 (16.20-36.40)	0.2	23.0 (19.35-27.15)	0.795
% BDR R20	22.70 (15.50-35.47)	25.70 (15.42-33.10)	0.483	17.50 (12.08-24.28)	0.174
% BDR of ALX	47.5 (31.32-71.4)	49.5 (29.9-58.4)	0.36	49.9 (29.2-66.2)	0.89
tVDD	**Baseline**	**1 month**	***P value**	**3 month**	**#P value**
R5 ($cmH_2O/L/S$)	6.47 (2.68)	6.12 (2.20)	0.263	6.25 (2.41)	0.411
R20 ($cmH_2O/L/S$)	5.81 (1.87)	5.48 (1.54)	0.145	5.60 (1.77)	0.314
X5 ($cmH_2O/L/S$)	-0.89 (-1.41 to -0.44)	-0.70 (-1.51 to -0.35)	0.360	-0.57 (-1.27 to -0.42)	0.095
R5-R20 ($cmH_2O/L/S$)	0.40 (0.07-1.17)	0.37 (0.1-1.29)	0.86	0.5 (0.22-1.08)	0.98
ALX (cmH_2O/L)	3.64 (1.41-7.49)	2.69 (1.14-8.67)	0.52	2.22 (1.37-6.46)	0.18
Fres (Hz)	9.6 (7.17-12.80)	9.05 (7.10-14.04)	0.66	-0.6 (-1.3 to -0.4)	0.41
% BDR R5	18.80 (12.70-24.0)	22.50 (10.30-31.80)	0.776	21.40 (10.80-29.10)	0.728
% BDR R20	16.60 (10.0-24.80)	17.20 (5.50-24.20)	0.777	20.60 (12.35-28.85)	0.616
% BDR of ALX	38.9 (23.66-68.55)	43.05 (32.35-60.77)	0.86	31.3 (15.05-55.45)	0.37
pVDD	**Baseline**	**1 month**	***P value**	**3 month**	**#P value**
R5 ($cmH_2O/L/S$)	6.73 (2.84)	6.04 (2.43)	0.002	6.13 (3.03)	0.129
R20 ($cmH_2O/L/S$)	5.95 (2.0)	5.49 (1.77)	0.005	5.52 (2.14)	0.088
X5 ($cmH_2O/L/S$)	-0.70 (-1.38 to -0.46)	-0.78 (-1.33 to -0.58)	0.737	-0.90 (-1.16 to -0.45)	0.940
R5-R20 ($cmH_2O/L/S$)	0.465 (0.21-1.22)	0.46 (-0.13 to 1.14)	0.06	0.48 (-0.1 to 0.77)	0.33
ALX (cmH_2O/L)	2.88 (1.66-7.71)	3.27 (2.01-7.07)	0.80	4.22 (1.62-5.5)	0.79
Fres (Hz)	9.26 (8.08-2.95)	9.29 (7.86-12.89)	0.48	10.24 (7.93-11.78)	0.95

Data presents as N (%), mean (sd) or median (IQR). nVDD = non-vitamin D deficiency, tVDD = vitamin D deficiency with treatment, pVDD = vitamin D deficiency with placebo, R5 = resistance at 5 Hz, R20 = resistance at 20 Hz, X5 = reactance at 5 Hz, ALX = area of reactance, Fres = resonance frequency and BDR = bronchodilator response. *comparison between baseline and 1 month visit, # comparison between baseline and 3 month visit

Table 3. (Continued)

pVDD	Baseline	1 month	*P value	3 month	#P value
% BDR of R5	27.40 (18.20-37.50)	24.20 (15.10-30.20)	0.670	24.9 (16.2-35.2)	0.679
% BDR R20	23.20 (14.65-31.60)	18.90 (10.70-24.70)	0.472	19.8 (15.9-27.1)	0.514
% BDR of ALX	47.9 (38.87-73.55)	54.3 (26.15-65.6)	0.18	40.4 (24.4-53.85)	0.1

Data presents as N (%), mean (sd) or median (IQR). nVDD = non-vitamin D deficiency, tVDD = vitamin D deficiency with treatment, pVDD = vitamin D deficiency with placebo, R5 = resistance at 5 Hz, R20 = resistance at 20 Hz, X5 = reactance at 5 Hz, ALX = area of reactance, Fres = resonance frequency and BDR = bronchodilator response. *comparison between baseline and 1 month visit, # comparison between baseline and 3 month visit

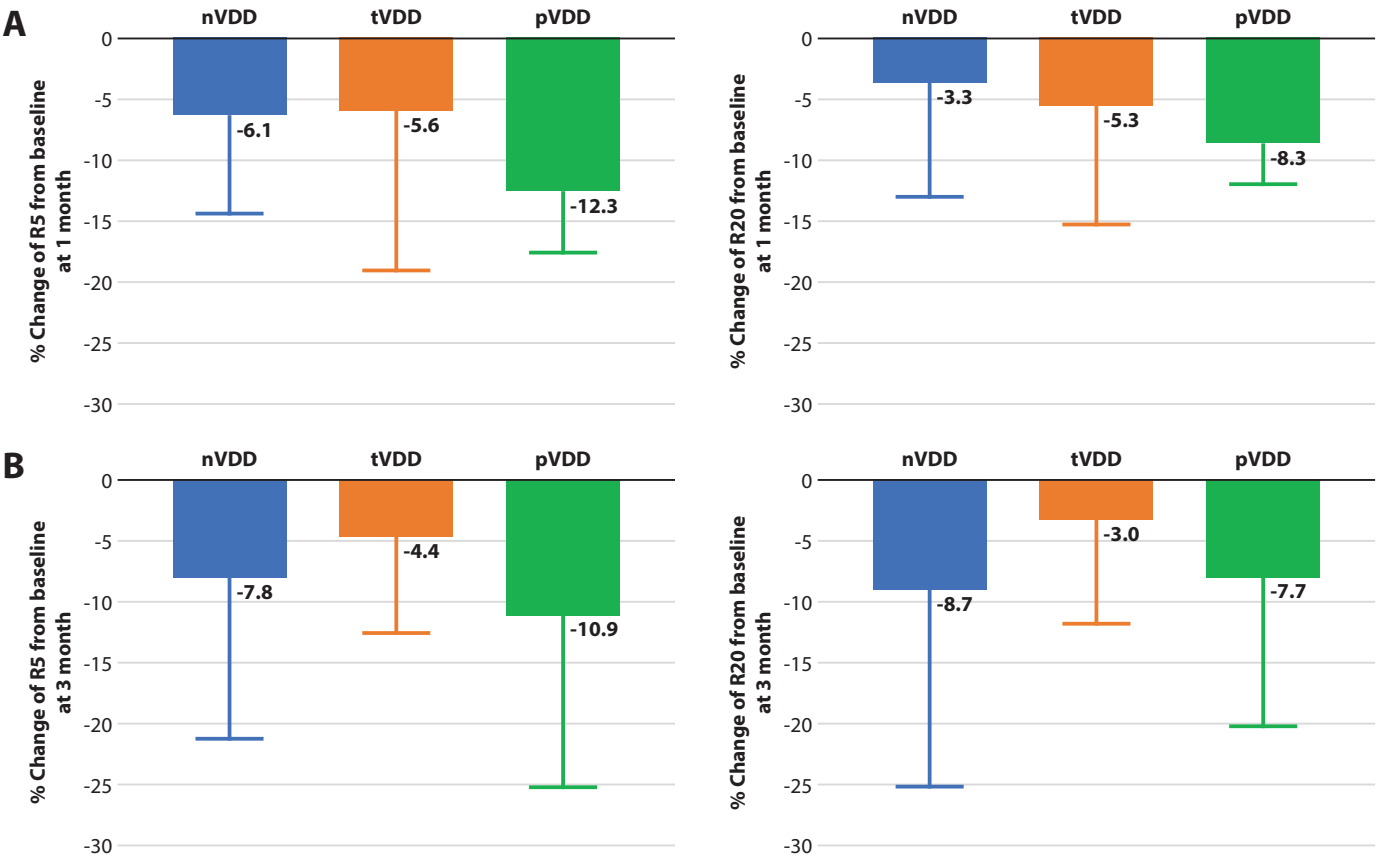

Figure 3. Percent change of resistance from baseline at 1 month (A) and 3 months (B).

changes of R5 and R20 from baseline values at 1 and 3 months were not significantly different among nVDD, tVDD and pVDD (**Figure 3**).

Association of vitamin D status and asthma control

There was no significant difference between nVDD group and VDD group in the level of asthma control and ACT/P-ACT score, aero-allergen sensitization, blood eosinophil and dosage of inhaled corticosteroid. There was no significant correlation between serum total 25 (OH)D level and % predicted of FOT parameter.

Discussion

We have shown that vitamin D deficiency is common in Thai asthmatic children. Almost half of children with controlled asthma in the current study have vitamin D deficiency which is similar to the prevalence of vitamin D deficiency in Thai children living in urban area.[16] The association of vitamin D and asthma have been reported both in children and adults.[17,18]

However, we did not find the association between the level of vitamin D and % predicted of FOT parameters in asthmatic children. The association of vitamin D level and lung function remains inconsistent. A study in Danish adults has shown the association of low level of vitamin D and lower % predicted FEV1 in the cross-sectional study but patients with higher serum vitamin D at baseline have shown to have more adverse change in % predicted FEV1 in 5 years later.[19] In contrast, Norwegian adults with asthma who had vitamin D deficiency at baseline was shown to have more decline in lung function measured by spirometry at 11 years later.[20] A recent cross sectional study have shown the association of FEV1 and vitamin D deficiency only in obese asthmatic children but not in asthmatic children with normal weight.[21] However, in subgroup

analysis comparing between enrolled children with normal weight and obese, no significant differences in FOT parameters were observed in the current study (data not shown).

The current study have found that vitamin D treatment in controlled asthmatic children who had vitamin D deficiency had no effect on FOT parameters over the 3 month-study period. Children in nVDD group showed a statistically improvement in R5, R20 and X5 after enrollment in the study but the changes in the FOT values may not have an impact on clinical outcome. Since the day-to-day variability of FOT values were reported to be 10–11%[22] and all of the changes in FOT values between visits are within 10-11%. However, there was no statistically significant changes in tVDD. A previous study demonstrated that asthmatic patients with low serum vitamin D level had reduce glucocorticoid response.[2] Asthmatic children who had vitamin D deficiency had lowest improvement of FEV1 after treatment with inhaled corticosteroid when compared to asthmatic children with non-vitamin D deficiency.[1] Our enrolled children who had vitamin D deficiency may have a reduced response to inhaled corticosteroid resulting in no improvement of FOT parameters over time compared to non-vitamin D deficiency group. However, children in VDD with vitamin D treatment group gained their non-vitamin D deficiency status after vitamin D treatment, but there were no significant improvements in FOT parameters at 1 month or 3 months following treatment. We speculate that vitamin D deficiency may have a detrimental effect on lung function longer than 3 months after gaining the status of non-vitamin D deficiency. Low serum vitamin D at birth[23] or low maternal vitamin D[24] have been shown to associate with higher airway resistance at the age of 6. A recent study in Japanese asthmatic children who received vitamin D supplementation for 2 months have shown the improvement in level of asthma control, peak expiratory flow at 6 months. Nevertheless, some of these Japanese asthmatic children were non-vitamin D deficiency , their mean serum vitamin D levels were 28.5 ng/ml in the intervention group and 29 ng/ml in the control group.[5] However, a recent study was shown that vitamin D supplementation for 6 months in adult asthma who had vitamin D insufficiency did not reduce the rate of asthma treatment failure or exacerbation and had no significant effects on lung function.[25] The discrepant findings for vitamin D and lung function may be explained by the differences in age, race/ethnicity, number of participants, and the status of vitamin D before enrollment. The strengths of our study are 1) all randomized patients were naive vitamin D deficient patients 2) having non-vitamin D deficient patients as a control group for the variable changes of FOT parameters over time. The limitations of the study are 1) relative small number of the enrolled children 2) 3 months follow up time may be too short to demonstrate the effect of vitamin D on lung function in previously untreated vitamin D deficient patients. However, a randomized clinical trial for vitamin D treatment for 28 weeks in adult asthma with low vitamin D showed no reduction in asthma exacerbation or improvement of lung functions.[25]

In conclusions, vitamin D treatment in asthmatic children who had vitamin D deficiency may have no short term beneficial effect on pulmonary function assessed by FOT. Recommendation for vitamin D supplementation in asthmatic patient needs further study.

Acknowledgements

This study was supported by the research grant from Faculty of Medicine Ramathibodi hospital, Mahidol University, Bangkok, Thailand.

Conflict of interest

The authors declare that they have no conflicts of interest.

References

1. Wu AC, Tantisira K, Li L, et al. Effect of vitamin D and inhaled corticosteroid treatment on lung function in children. Am J Respir Crit Care Med 2012;186:508-13.
2. Sutherland ER, Goleva E, Jackson LP, Stevens ADLeung DY. Vitamin D levels, lung function, and steroid response in adult asthma. Am J Respir Crit Care Med 2010;181:699-704.
3. Brehm JM, Schuemann B, Fuhlbrigge AL, et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. J Allergy Clin Immunol 2010;126:52-8.
4. Lewis E, Fernandez C, Nella A, et al. Relationship of 25-hydroxyvitamin D and asthma control in children. Ann Allergy Asthma Immunol 2012; 108:281-2.
5. Tachimoto H, Mezawa H, Segawa T, et al. Improved control of childhood asthma with low-dose, short-term vitamin D supplementation: a randomized, double-blind, placebo-controlled trial. Allergy 2016;71: 1001-9.
6. Martineau AR, Cates CJ, Urashima M, et al. Vitamin D for the management of asthma. Cochrane Database Syst Rev 2016;9:CD011511.
7. Krobtrakulchai W, Praikanahok J, Visitsunthorn N, et al. The effect of vitamin d status on pediatric asthma at a university hospital, Thailand. Allergy Asthma Immunol Res 2013;5:289-94.
8. Brashier BSalvi S. Measuring lung function using sound waves: role of the forced oscillation technique and impulse oscillometry system. Breathe 2015;11:57.
9. Moeller A, Carlsen KH, Sly PD, et al. Monitoring asthma in childhood: lung function, bronchial responsiveness and inflammation. Eur Respir Rev 2015;24:204-15.
10. Skylogianni E, Douros K, Anthracopoulos MBFouzas S. The Forced Oscillation Technique in Paediatric Respiratory Practice. Paediatr Respir Rev 2016;18:46-51.
11. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-30.
12. Sommanus S, Direkwattanachai C, Lawpoolsri SSitcharungsi R. Accuracy of childhood asthma control test among Thai childhood asthma patients. Asian Pac J Allergy Immunol 2018;36:152-58.
13. Schatz M, Sorkness CA, Li JT, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol 2006;117:549-56.
14. Liu AH, Zeiger R, Sorkness C, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol 2007;119:817-25.
15. Majak P, Olszowiec-Chlebna M, Smejda KStelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. J Allergy Clin Immunol 2011;127:1294-6.
16. Rojroongwasinkul N, Kijboonchoo K, Wimonpeerapattana W, et al. SEANUTS: the nutritional status and dietary intakes of 0.5-12-year-old Thai children. Br J Nutr 2013;110 Suppl 3:S36-44.
17. Hollams EM, Teo SM, Kusel M, et al. Vitamin D over the first decade and susceptibility to childhood allergy and asthma. J Allergy Clin Immunol 2017;139:472-81.
18. Mulrennan S, Knuiman M, Walsh JP, et al. Vitamin D and respiratory health in the Busselton Healthy Ageing Study. Respirology 2018;23: 576-82.
19. Thuesen BH, Skaaby T, Husemoen LL, et al. The association of serum 25-OH vitamin D with atopy, asthma, and lung function in a prospective study of Danish adults. Clin Exp Allergy 2015;45:265-72.

20. Brumpton BM, Langhammer A, Henriksen AH, et al. Vitamin D and Lung Function Decline in Adults With Asthma: The HUNT Study. Am J Epidemiol 2016;183:739-46.
21. Lautenbacher LA, Jariwala SP, Markowitz MERastogi D. Vitamin D and pulmonary function in obese asthmatic children. Pediatr Pulmonol 2016; 51:1276-83.
22. Oostveen E, Macleod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J 2003;22:1026-41.
23. Gazibara T, Den Dekker HT, De Jongste JC, et al. Associations of maternal and fetal 25-hydroxyvitamin D levels with childhood lung function and asthma: the Generation R Study. Clin Exp Allergy 2016;46:337-46.
24. Zosky GR, Hart PH, Whitehouse AJ, et al. Vitamin D deficiency at 16 to 20 weeks' gestation is associated with impaired lung function and asthma at 6 years of age. Ann Am Thorac Soc 2014;11:571-7.
25. Castro M, King TS, Kunselman SJ, et al. Effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial. JAMA 2014;311:2083-91.