

A randomised trial of vitamin D in acute-stage allergic bronchopulmonary aspergillosis complicating asthma

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Summary

Vitamin D has been demonstrated to have an immunomodulatory role in cystic fibrosis with allergic bronchopulmonary aspergillosis (ABPA). Herein, we evaluate supplemental vitamin D in acute-stage ABPA complicating asthma. Thirty subjects were randomised to receive either prednisolone ($n = 15$, control) or prednisolone and oral vitamin D ($n = 15$, intervention arm). Serum vitamin D levels were significantly higher in the intervention versus the control arm, following therapy. The mean decline in total IgE at 2 months (primary outcome) was 10% higher in the intervention arm than the control arm; however, this was not statistically significant (48.6% vs 38.1%, $P = 0.27$). The percentage decline in total IgE after 4 and 6 months of randomisation was also similar in the two arms. There was no difference in asthma exacerbations (0 vs 2, intervention vs control; $P = 0.16$). No ABPA exacerbation occurred in either arm. The other outcomes including the Th2 (IL-4, IL-6 and IL-10) and Th17 (IL-17) cytokine levels were similar in the two groups. None of the participants experienced hypervitaminosis D. There was no significant improvement in the clinical or immunological outcomes following vitamin D supplementation. A larger trial is required to ascertain the role of vitamin D in ABPA complicating asthma [Clinicaltrials.gov: NCT03133299].

KEYWORDS

ABPM, asthma exacerbation, cholecalciferol, immunotherapy, severe asthma

1 | INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is an immunological disorder caused by hypersensitivity reactions against *Aspergillus fumigatus*.¹ It usually complicates the course of individuals with bronchial asthma or cystic fibrosis (CF). A heightened Th2 response against the antigens of *A. fumigatus* is the pathogenetic hallmark of ABPA.² Vitamin D receptors are expressed in all immune cells and regulate innate as well as adaptive immunity.³ Vitamin D deficiency has been shown to cause upregulation of Th2 cytokines, and

exaggerated response to allergens.⁴ There is an association between low vitamin D levels and poor asthma control.⁵ There is also an association between vitamin D deficiency and ABPA in patients with CF.⁶

A combination of dexamethasone and vitamin D favourably modulates the functioning of regulatory T cells,⁷ which are essential in establishing immune tolerance to *A. fumigatus* antigens. Recently, the safety of supplemental vitamin D and its immunomodulatory potential was demonstrated in CF patients with ABPA.⁸ Whether supplemental vitamin D is also effective in asthmatics with ABPA and remains unknown. We hypothesised that the administration of adjunctive vitamin D (in addition to the standard systemic glucocorticoid therapy) would lead to a better immunological response in

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acute-stage ABPA complicating asthma. Herein, we study the efficacy and safety of supplemental vitamin D therapy in subjects with ABPA complicating asthma.

2 | METHODS

The current study was an investigator-initiated, prospective, open-label, parallel group randomised controlled trial (RCT) conducted between January 2017 and June 2018 at the Chest Clinic of this institute. The study protocol was approved by the Institute Ethics Committee, and a written informed consent was obtained from all the subjects. The trial was registered at www.clinicaltrials.gov (NCT03133299). The results are reported as per the CONSORT statement.⁹

2.1 | Patient selection

Subjects aged ≥ 12 years were eligible for inclusion in the trial, if they met all of the following: (1) asthma; (2) serum *A fumigatus*-specific IgE > 0.35 kUA/L; (3) serum total IgE > 1000 IU/mL (subjects with total IgE < 1000 IU/mL were included, if all the other criteria were satisfied and high-attenuation mucous [HAM] was identified on computed tomography); and, two of the following: (i) serum *A fumigatus*-specific

IgG > 27 mgA/L, (ii) transient or fixed radiographic lung opacities; and, (iii) peripheral blood eosinophilia > 500 cells/ μ L.¹⁰

We excluded participants if they met any of the following: (a) intake of systemic glucocorticoids for > 3 weeks in the preceding 6 months; (b) serum creatinine ≥ 1.5 mg/dL or the estimated glomerular filtration rate < 60 mL/min; (c) pregnancy or lactating women; (d) hepatitis B or hepatitis C or human immunodeficiency virus infection; (e) serum calcium > 11 mg/dL, plasma 25-hydroxy vitamin D > 50 ng/mL; (f) treatment with antifungal triazoles or omalizumab; (g) chronic liver disease, chronic renal disease, uncontrolled diabetes mellitus, and treatment with cytotoxic therapies; and, (h) failure to provide informed consent.

2.2 | Randomisation

It was performed using a computer-generated sequence, and the assignments were placed in opaque sealed envelopes. Consecutive subjects meeting the inclusion criteria were randomised 1:1 to either the control arm or the intervention arm. The study was not blinded.

2.3 | Study protocol

At baseline, we recorded the detailed clinical history and physical examination of the study participants. All investigations including

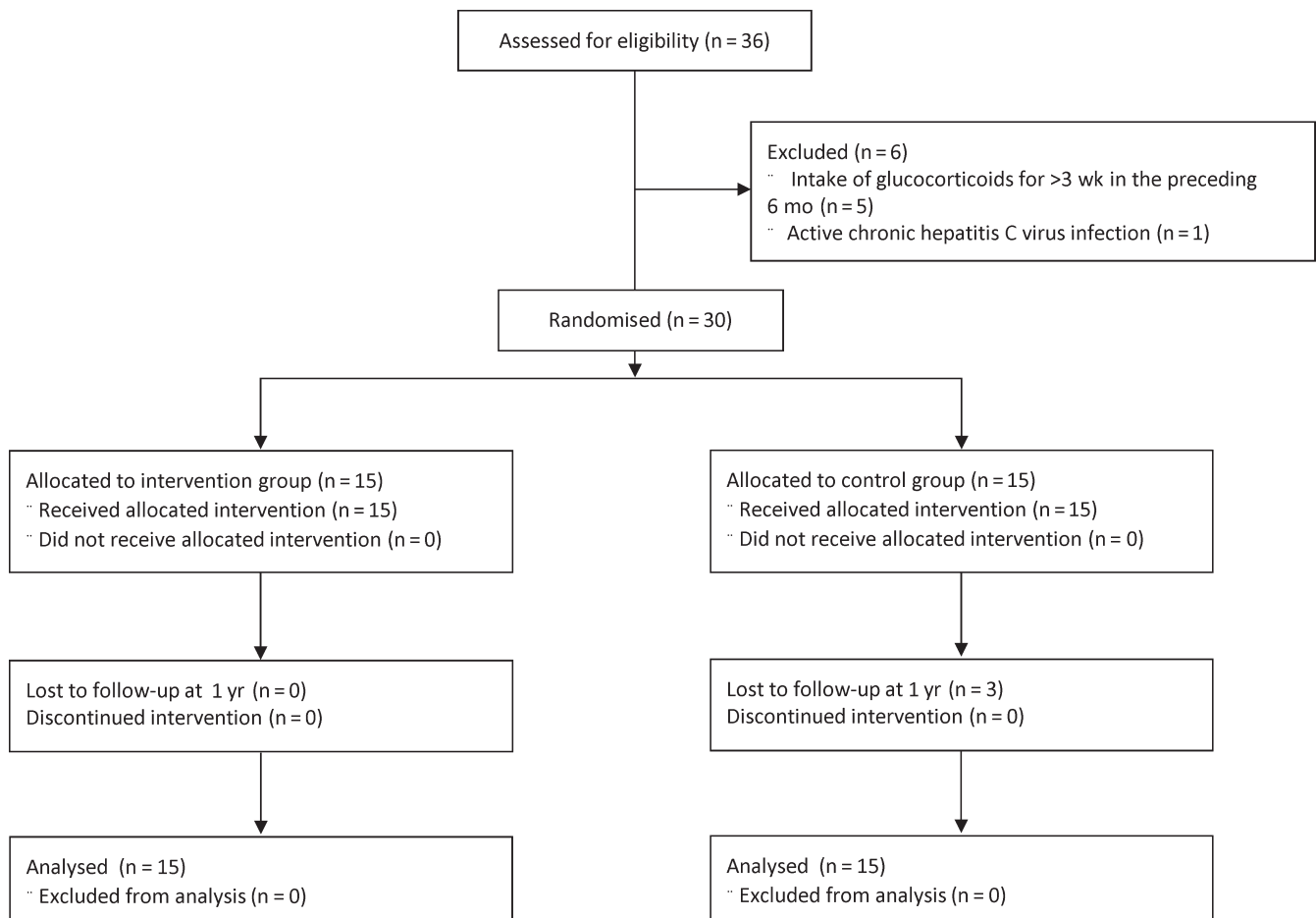


FIGURE 1 CONSORT diagram depicting the flow of participants in the study

TABLE 1 Baseline characteristics of the study participants

Characteristics	Intervention group (n = 15)	Control group (n = 15)	Total (n = 30)	P value
Demographic variables				
Age in years**	33 (12.5)	32 (12.2)	32.8 (12.1)	0.83
Male gender	11 (73.3)	10 (66.7)	21 (70)	0.50
Duration of asthma, y*	8 (0.3-25)	7 (0.7-25)	8 (0.33-25)	0.90
Family history of asthma	2 (13.3)	7 (46.6)	9 (30)	0.54
Symptoms				
Cough	15 (100)	14 (93.3)	29 (96.7)	0.50
Wheeze	14 (93.3)	15 (100)	29 (96.7)	0.24
Dyspnoea	13 (86.6)	15 (100)	28 (93.3)	0.35
Chest tightness	10 (66.6)	8 (53.3)	18 (60)	0.50
Sputum	5 (33.3)	6 (40)	11 (36.7)	0.22
Brownish-black sputum	2 (13.3)	5 (33.3)	7 (23.3)	0.22
Haemoptysis	0	2 (13.3)	2 (6.7)	0.22
Weight loss	2 (13.3)	1 (6.7)	3 (10)	0.49
Fever	3 (20)	2 (13.3)	5 (16.7)	0.50
Spirometry**				
FEV ₁ , L	2.10 (0.79)	1.96 (0.77)	2.03 (0.77)	0.65
FVC, L	2.95 (0.84)	2.91 (0.77)	2.93 (0.84)	0.90
FEV ₁ /FVC	69.7 (10.7)	66.3 (13.8)	68 (12.3)	0.45
Severity of obstruction				
Normal (FEV1 >80%)	6 (40)	4 (26.7)	10 (33.3)	0.35
Mild (FEV1 60-80%)	3 (20)	5 (33.3)	8 (26.7)	0.34
Moderate (FEV1 40-60%)	5 (33.3)	4 (26.7)	9 (30)	0.50
Severe (FEV1 <40%)	1 (6.7)	2 (13.3)	3 (10)	0.51
Chest HRCT findings				
Bronchiectasis	12 (80)	8 (53.3)	20 (66.7)	0.23
High-attenuation mucous	4 (26.7)	1 (6.7)	5 (16.7)	0.33
Investigations*				
<i>A. fumigatus</i> -specific IgE, kUA/L	33.9 (2.1-87.5)	23.2 (1.2-85.3)	30.4 (1.2-87.5)	0.64
<i>A. fumigatus</i> -specific IgG, mgA/L	111 (20.8-200)	77 (8.4-200)	90.7 (8.4-200)	0.17
Total eosinophil count, cells/ μ L	485 (100-2221)	680 (60-1788)	620 (66-2221)	0.39
Total IgE, IU/mL	6124 (419-35 435)	9194 (1802-17 820)	7487 (419-35 435)	0.88
Plasma 25-hydroxyvitamin-D, ng/dL	21.5 (6.1-41.6)	16.4 (5.4-41.1)	21.3 (5.4-41.6)	0.41
Calcium, mg/dL	9.2 (8-10.2)	9.5 (8.2-10.3)	9.3 (8-10.3)	0.13
Phosphorus, mg/dL	3.8 (3.2-4.5)	3.4 (2.1-4.8)	3.6 (2.1-4.8)	0.13
Albumin, mg/dL	4.1 (3.7-4.9)	4.2 (3.5-4.8)	4.2 (3.5-4.9)	0.37
Alkaline phosphatase, U/L	120 (74-189)	88 (53-123)	108 (53-189)	0.01
Vitamin D deficiency	6 (40)	6 (40)	12 (40)	0.46
Asthma treatment				
Subjects receiving ICS	15 (100)	15 (100)	30 (100)	0.98
Subjects receiving LABA	15 (100)	15 (100)	30 (100)	1.0
Subjects receiving LTRA	7 (50)	10 (66.7)	17 (58.6)	0.46

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting β 2 agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.

Data presented as *median (range) or **mean (SD).

All values are presented as numbers (percentages) unless mentioned otherwise.

TABLE 2 Primary and secondary outcomes

Outcome	Intervention group (n = 15)	Control group (n = 15)	P value
Primary outcome			
Percentage decline in total IgE after 2 mo of treatment	48.7 (36.5-60.9)	38.1 (20.6-55.6)	0.27
Secondary outcomes			
Percentage decline in total IgE after 4 mo of treatment	20.2 (5.5-34.9)	18.8 (2.3-35.4)	0.90
Percentage decline in total IgE after 6 mo of treatment	8.6 (-13.4 to 30.6)	9.9 (-8.3 to 28.1)	0.93
Number of ABPA exacerbations, n (%)	0	0	—
Number of asthma exacerbations, n (%)	0	2 (13.3)	0.16
Adverse effects of vitamin D supplementation, n (%)	0	0	—
Adverse events attributed to glucocorticoids, n (%)			
Hyperglycaemia	1 (6.7)	0	1.00
Abnormal fat deposition	2 (13.3)	0	0.48
Cutaneous striae	1 (6.7)	0	1.00
Plasma 25-hydroxyvitamin-D level in ng/dL			
After 1 mo	40.9 (30.7-51)	21.7 (11.8-31.6)	0.01
After 2 mo	44 (31.2-56.7)	22.3 (9.7-34.8)	0.02
After 3 mo	38.7 (26.2-51.2)	34.6 (10.6-58.6)	0.70

ABPA, allergic bronchopulmonary aspergillosis.

The values are presented as mean (95% CI) unless otherwise mentioned.

IgE and IgG against *A. fumigatus*, total IgE levels, peripheral blood eosinophil count, serum calcium, routine biochemical investigations, spirometry, chest radiograph, and high-resolution computed tomography (HRCT) of the thorax were performed, as described previously.¹¹⁻¹⁶ Plasma 25-hydroxyvitamin-D levels were measured using a competitive electro-chemiluminescence immunoassay on a fully automated analyzer (E 601, Roche Diagnostics, GmbH, Mannheim, Germany). Plasma 25-hydroxyvitamin-D level ≥ 30 ng/dL and < 20 ng/dL were labelled as normal and deficiency, respectively. We also measured the Th2 (IL-4, IL-6 and IL-10), and Th17 (IL-17) cytokines using the bead array technology with the commercially available BD™ Cytometric Bead Array (CBA) human Th2/Th17 cytokine Kit (Becton, Dickinson and Company, New Jersey, USA) according to the manufacturer's instructions.

2.4 | Intervention

The participants in both the groups received oral prednisolone 0.5 mg/kg/d for 4 weeks, followed by 0.25 mg/kg/d and 0.125 mg/kg/d for 4 weeks each. Prednisolone was then tapered by 5 mg every 2 weeks and discontinued subsequently.¹⁷⁻¹⁹ The total duration of prednisolone was 4 months. The subjects randomised to the intervention arm additionally received vitamin D supplementation (oral capsule of cholecalciferol 60 000 IU) once weekly for 8 weeks. We allowed participants in both the groups to receive inhaled corticosteroids, leukotriene receptor antagonists, long and short-acting

beta-2 agonists, for asthma control, as per the discretion of the treating physician.

2.5 | Monitoring

The patients were monitored for a period of 1 year after completion of treatment. At each visit, we documented improvement in the symptoms of cough and dyspnoea using a 4-point scale semi-quantitatively as 1: no improvement or worsening; 2: mild improvement (up to 25% reduction from the baseline); 3: moderate improvement (25%-75% reduction from the baseline); 4: significant improvement ($> 75\%$ reduction from the baseline), as previously described.¹⁷⁻¹⁹ Adverse events related to treatment were enquired (eg, hypertension, hyperglycaemia, weight gain, purple striae and others). We performed a chest radiograph and total IgE every 2 months for 6 months. The interleukin levels were measured at baseline, 2, 4 and 6 months after randomisation. Plasma 25-hydroxyvitamin-D level and calcium profile (serum calcium, phosphate, albumin and alkaline phosphatase) were estimated monthly for the initial 3 months after randomisation.

2.6 | Definitions

Response to treatment was defined as an improvement in cough and dyspnoea ($> 75\%$ of baseline) accompanied by a major (at least 50%) clearance of chest radiographic opacities (if present

TABLE 3 Cytokine levels at baseline and during follow-up in the study participants

Cytokines	Intervention arm				Control arm			
	Baseline	2 mo	4 mo	6 mo	Baseline	2 mo	4 mo	6 mo
Th2 cytokines								
IL-4	13.5 (3.1-58.5)	5.2 (1.1-61.8)	11.1 (2.1-37.5)	8.7 (0-45)	23.6 (6.4-106.3)	11 (6.4-42.2)	16.1 (2.1-89.9)	12.3 (2.1-25.7)
IL-6	84.6 (9-150.2)	22.9 (16.5-235.2)	25 (18.5-121.7)	25.5 (5.2-42.9)	44.5 (27.2-219.9)	60.1 (10.3-235.2)	65.2 (17-724.3)	15.5 (9-300)
IL-10	7.9 (7.9-7.9)	17.7 (17.7-17.7)	21.5 (6.3-36.8)	7.9 (4.3-31.8)	19 (12.4-251)	89.8 (17.8-162)	18 (13.8-26.4)	11 (1-31.8)
Th17 cytokine								
IL-17	137 (37.7-684.1)	68 (45.6-260)	64.3 (5.8-240.8)	103.6 (29.4-393.6)	277 (145.3-301.2)	62.9 (20-887.1)	138.4 (0-240.8)	393.6 (393.6-393.6)

IL, interleukin; Th2, type 2 T helper cells; Th17, T helper 17 cells.

All values are presented as median (range) in pg/mL.

None of the cytokines showed a significant difference within and between subjects at baseline or during follow-up.

before treatment initiation), along with a decline in serum total IgE by $\geq 25\%$, after 2 months of treatment. *ABPA exacerbation* was defined as clinical and/or radiological worsening along with 50% increase in the serum total IgE levels from the previous baseline value. Clinical worsening (cough, dyspnoea and wheeze) alone, in the absence of radiological and immunological criteria, was termed as *asthma exacerbation*.

2.7 | Outcomes

The *primary outcome* was the percentage decline in serum total IgE ($[\text{baseline total IgE} - \text{new total IgE level}] / \text{baseline total IgE}$, expressed as a percentage) after 2 months of randomisation. The *secondary outcomes* were as follows: (a) percentage decline in total IgE after 4 and 6 months of randomisation (compared to the IgE values at the most recent follow-up); (b) number of asthma and ABPA exacerbations over the follow-up period of 1 year; and, (d) adverse events related to treatment. The other outcomes included the following: (a) plasma 25-hydroxyvitamin-D levels after 1, 2 and 3 months after randomisation; and, (b) Th2 and Th17 cytokine levels at baseline, and 2, 4 and 6 months after randomisation.

2.8 | Sample size estimation

The expected decline in total IgE level following 2 months of glucocorticoid therapy (primary outcome) is about 25%. We hypothesised that vitamin D would improve immunological outcome, and we expected an additional 10% decline in total IgE after vitamin D supplementation (intervention arm). To detect this difference, we would require 330 subjects in each arm (power 80% and alpha 0.05). We planned an exploratory study recruiting 15 subjects in each arm.

2.9 | Statistical analysis

We used the commercial statistical package (SPSS for Windows, version 22.0; IBM SPSS Inc; Chicago, IL) for performing the statistical analysis. Categorical data are presented as numbers (percentage) and continuous data as mean (95% confidence interval [CI]) or median (range). The differences between categorical and continuous variables were analysed using the chi-squared test and the Mann-Whitney *U* test, respectively. For outcome analysis, we included all the participants who were randomised (intention-to-treat). A *P*-value < 0.05 was considered as statistically significant.

3 | RESULTS

We screened 36 consecutive subjects of asthma with ABPA (Figure 1), of which 30 were randomly assigned to either the intervention arm ($n = 15$) or the control arm ($n = 15$). The follow-up period of 1 year was completed in all except three subjects in the control arm. All these three subjects were lost to follow-up after 1 month of randomisation. None of the other participants in either group

TABLE 4 Primary and secondary outcomes in vitamin D-deficient (<20 ng/dL) subgroup

Outcomes in vitamin D-deficient subgroup	Intervention group (n = 6)	Control group (n = 6)	P value
Primary outcome			
Percentage decline in total IgE after 2 mo of treatment	57.7 (33.9-81.5)	40.9 (11.7-70.1)	0.28
Secondary outcomes			
Percentage decline in total IgE after 4 mo of treatment	20.7 (-8.1 to 49.4)	2 (-11.1 to 15)	0.19
Percentage decline in total IgE after 6 mo of treatment	18.2 (-15.6 to 51.9)	8.8 (-22.3 to 39.9)	0.59
Number of ABPA exacerbations, n (%)	0	0	—
Number of asthma exacerbations, n (%)	0	2	0.18
Adverse effects of vitamin D supplementation, n (%)	0	0	—
Adverse events attributed to glucocorticoids, n (%)			
Hyperglycaemia	1 (13.3)	0	1.00
Abnormal fat deposition	1 (13.3)	0	1.00
Cutaneous striae	1 (13.3)	0	1.00

ABPA, allergic bronchopulmonary aspergillosis.

Values are presented as mean (95% CI) unless otherwise mentioned.

discontinued therapy. The baseline characteristics were similar in the two groups (Table 1). The mean (SD) age of the subjects was 32.8 (12.1) years. Most participants had long-standing asthma with a median (range) duration of 8 (0.3-25) years. Spirometry showed mild or moderate obstruction in nearly half of the study participants (n = 17, 56.7%). Bronchiectasis and high-attenuation mucus on HRCT thorax were identified in 66.7% (n = 20) and 16.7% (n = 5), respectively. The median (range) total IgE, total eosinophil count, serum calcium, and plasma 25-hydroxyvitamin-D levels at baseline were 7487 (419-35 435) IU/mL, 620 (66-2221) cells/ μ L, 9.3 (8-10.3) mg/dL, and 21.3 (5.4-41.6) ng/dL respectively. All the study participants were receiving inhaled corticosteroids and long-acting β -agonist, while 58.6% (n = 17) were also being treated with leukotriene receptor antagonists.

Plasma 25-hydroxyvitamin-D levels increased significantly in the intervention arm as compared to the control arm after 1 and 2 months of supplementation. The mean (95% CI) percentage decline in total IgE at 2 months of therapy was 48.7 (36.5-60.9) and 38.1 (20.6-55.6) in the intervention and control groups, respectively (P = 0.27). No ABPA exacerbations occurred during follow-up. Two patients in the control arm and none in the intervention arm experienced exacerbation of bronchial asthma; this difference was, however, not statistically significant (P = 0.16). The percentage decline in total IgE after 4 and 6 months of randomisation was also similar in both the arms (Table 2). None of the study participants in the intervention arm experienced adverse effects related to vitamin D supplementation. Adverse events related to glucocorticoid therapy were not different in the two groups (Table 2). The cytokine levels at baseline, 2, 4 and 6 months of randomisation were similar in the two groups (Table 3).

Of the 30 subjects included in the trial, vitamin D deficiency (<20 ng/dL) at baseline was found in 12 (6 in each of the study groups). We performed a subgroup analysis including only the vitamin D-deficient subjects (n = 12). In the intervention arm, the decline in IgE was higher than the control arm by 16%, 18% and 10.6% at 2, 4 and 6 months after randomisation (Table 4). However, none of the outcomes were significantly different between the two groups.

4 | DISCUSSION

The results of this exploratory study suggest no additional benefit of supplemental vitamin D in the clinical or immunological response to glucocorticoid therapy in acute-stage ABPA complicating asthma.

Vitamin D has been shown to play an immunomodulatory role in CF subjects with ABPA. In 1 study, costimulatory molecule OX40 ligand was found to be one of the factors responsible for Th2 skewing of CD4+ T cells, whereas individuals without ABPA had higher T-regulatory cells expressing TGF- β .⁶ Vitamin D was shown to reduce OX40 ligand expression and increase TGF- β expression in vitro.⁶ Further, individuals with CF and ABPA had a higher prevalence of vitamin D deficiency, probably due to malabsorption.⁶ In the only available study evaluating the role of vitamin D in ABPA, 4000 IU of vitamin D was administered daily for 24 weeks in seven CF subjects with ABPA.⁸ Vitamin D supplementation was safe, and decreased the *Aspergillus*-induced IL-13 (Th2 cytokine) response from CD4+ T cells in vitro.¹⁵

Unlike CF, the prevalence of vitamin D deficiency has been shown to be similar in asthmatic patients with and without ABPA.²⁰

²¹ We had hypothesised that supraphysiological doses of vitamin D could be beneficial in reversing Th2 inflammation seen in patients with ABPA. However, we did not find any difference in the Th2 cytokine levels between the two groups in the present study. We measured the IL-4, IL-6, IL-10 and IL-17 at baseline and during follow-up, unlike the previous study which assessed the in vitro decline in IL-13 levels only.⁸ Although Nguyen et al found a decline in *A. fumigatus*-specific IgE after adjunctive vitamin D,¹⁵ it is known that *A. fumigatus*-specific IgE is a poor marker for response assessment in ABPA.¹⁴

What does our study add to the existing data? To our knowledge, the current study is the first RCT exploring the utility of supplemental vitamin D in ABPA complicating asthma. The prospective nature of the research, and the long duration of follow-up are strengths of our study while the lack of blinding and the absence of a placebo are limitations. Despite achieving a significantly higher vitamin D levels in the intervention arm, we did not find any statistically significant difference in the outcomes between the two groups. The immunological effects of vitamin D could have been explored further by measuring the T-regulatory cell activity, which was not performed in the current study. Although in vitro evidence of favourable immune modulation may have suggested a potential role of adjunctive vitamin D in ABPA, the clinical practice would not change unless its efficacy is proven in patients. In this context, the primary and secondary outcomes in our study were clinically relevant. There were two asthma exacerbations over 1 year, and both occurred in the control group. Also, both these patients were vitamin D-deficient at enrolment. Whether supplementation could improve the outcomes in vitamin D-deficient subjects is not clear. Although the subgroup analysis of vitamin D-deficient subjects did not reveal any difference, our study was not powered for such an analysis. For the sample size calculation, we expected an additional 10% decline in total IgE levels after 2 months of treatment in the experimental group. We did observe a greater than 10% decline in the intervention arm vis-à-vis the control arm, although this was not statistically significant. It is possible that our sample size was too small to detect this difference. Interestingly, when we analysed the effect of vitamin D supplementation in vitamin D-deficient subjects, the decline in total IgE levels was even greater (about 17% higher in the intervention arm vs the control arm) and more sustained over the next 6 months. Whether alternative regimens of vitamin D supplementation (such as daily supplementation) or longer duration of therapy would have yielded a different result, also remains uncertain.

In conclusion, the current study did not find any significant clinical and immunological improvement with vitamin D supplementation. However, there may be a potential benefit in vitamin D-deficient subjects with ABPA, and this needs to be evaluated in future studies.

CONFLICTS OF INTEREST

None.

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