

Letter to the Editor

Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection

To the Editor:

Previous studies suggest that vitamin D may play a role in the pathogenesis of asthma.¹ On the basis of the results of recent cross-sectional and basic scientific studies in this subject matter, we can speculate that vitamin D supplementation may (1) prevent the development of asthma, (2) reduce the risk of a more severe disease, and (3) enhance clinical response to glucocorticosteroids. However, none of these hypotheses have been verified so far. Taking into account deficiency of vitamin D in the asthmatic population,² the results of clinical trials concerning vitamin D supplementation seem to be of high clinical importance.¹ In the current study, we aimed to assess the effects of vitamin D supplementation on symptom score, lung function, and the number of exacerbations in children with newly diagnosed asthma.

Forty-eight children from 5 to 18 years of age (mean [SD], 11.5 [3.3] years) with newly diagnosed asthma and sensitive only to house dust mites were recruited from our allergy clinic center. All patients followed a recommended diet and performed physical exercises appropriate for school-age children.³ The main exclusion criteria were treatment with an oral, inhaled, or intranasal corticosteroid and supplementation with vitamin D during the 6 months preceding the trial, a history of fractures in the last 2 years, immunotherapy, obesity (body mass index >30 kg/m²), and other chronic diseases. The study was approved by the ethics committee. This was a randomized, double-blind, parallel-group, 6-month trial studying the effects of inhaled budesonide with or without vitamin D on clinical parameters of asthma control in children. There were 2 main study visits and 2 additional interview visits. The first visit was scheduled between September 2007 and February 2008. The patients were informed about the aim of the study and were instructed on how to use the inhalers and how to complete the Asthma Therapy Assessment Questionnaire (ATAQ) for children.⁴ During the first visit, the patients were randomized according to a computer-generated allocation schedule. The 2 resulting groups received treatment with the following: (1) budesonide 800 µg/d administered as a dry powder and vitamin D placebo (steroid group; $n = 24$), and (2) budesonide 800 µg/d administered as a dry powder and vitamin D-500 IU cholecalciferol (steroid + D3 group; $n = 24$). During the main study visits, the 2 following procedures were performed at the same time of the day, between 9 AM and 12 PM, before the morning dose of ICS: blood sampling (5 mL) for 25-hydroxyvitamin D (25(OH)D) measurement and spirometry (Jaeger MasterScreenBody; E Jaeger GmbH; Wurzburg, Germany) for the measurement of FEV₁. During the additional interview visits (2 and 4 months after the first visit), ATAQ scores were collected and evaluated for each month separately. Compliance with asthma medication was checked; the patients were asked to bring all used and unused medication to each follow-up visit. The level of serum 25(OH)D was determined by using a specific radioimmunoassay (25-OH-vit.D3-RIA-CT; BioSource Europe SA, Nivelles, Belgium). To determine differences within and between the groups, ANOVA for repeated measurements was used (Statistica for Windows, release 6.0; StatSoft, Inc, Tulsa, Okla). All

TABLE I. Baseline characteristics*

Baseline characteristics	Steroid group (n = 24)	Steroid + D3 group (n = 24)
Age (y)	11.1 (3.3)	10.8 (3.2)
Male sex, n (%)	18 (75)	14 (58.3)
BMI (kg/m ²)	18.8 (3.5)	18.5 (4.7)
FEV ₁ (% predicted)	98.7 (12)	94.4 (13)
ATAQ score	3.43 (0.88)	3.08 (0.88)

BMI, Body mass index.

*Unless otherwise indicated, data are presented as mean (SD).

TABLE II. Within-group comparisons of study endpoint

	Before treatment	After treatment	
Study outcome	Mean (SD)	Mean (SD)	P level
Steroid group			
ATAQ score (points)	3.43 (0.88)	0.33 (0.23)	<.001
FEV ₁ (% predicted)	98.7 (12)	103.1 (12.1)	.003
25(OH)D (ng/mL)	35.1 (16.9)	31.9 (12.1)	.25
Steroid + D3 group			
ATAQ score (points)	3.08 (0.88)	0.63 (0.23)	<.001
FEV ₁ (% predicted)	94.4 (13.0)	99.0 (11.1)	.002
25(OH)D (ng/mL)	36.1 (13.9)	37.6 (13.1)	.26

patients completed the study. The characteristics of the patients are presented in Table I. At the starting point of the study, there were no statistically significant differences between the 2 treatment groups regarding any of the study endpoints. When the study ended, we found that during 6 months of treatment, the number of children who experienced asthma exacerbation was significantly lower in the steroid + D3 group than in the steroid group (n [%], 4 [17] vs 11 [46]; $P = .029$; Fig 1, B). Despite the lack of any significant difference between the study groups as far as the absolute changes of 25(OH)D (Fig 1) were concerned, the number of children with a decrease of 25(OH)D was significantly lower in the steroid + D3 group than the steroid group (Fig 1, B). Logistic regression analysis showed that the number of exacerbations, as a dependent variable, is associated with 25(OH)D serum level. In children with a decrease of 25(OH)D, the risk of asthma exacerbation was 8 times higher than in children with a stable or increased 25(OH)D serum level (odds ratio, 8.6; 95% CI, 2.1-34.6).

After 6 months of treatment, a significant improvement in ATAQ score and FEV₁ was observed in both study groups (Table II). The difference between the groups in ATAQ score was observed in only 1 month (Fig 2, A). The improvement in FEV₁ was the same for both groups. A significant linear correlation between baseline 25(OH)D serum level and baseline ATAQ score ($R = -.372$; $P = .009$) was discovered. Children with lower baseline 25(OH)D had more severe clinical manifestations of asthma. All cases of asthma exacerbation were preceded by symptoms of an acute respiratory infection; short-acting β_2 -agonists and antibiotics (if appropriate) were implemented; none of our patients required hospitalization or intensification of anti-inflammatory therapy during the study.

This is the first prospective study showing that the control of newly diagnosed asthma in children can be facilitated by vitamin D

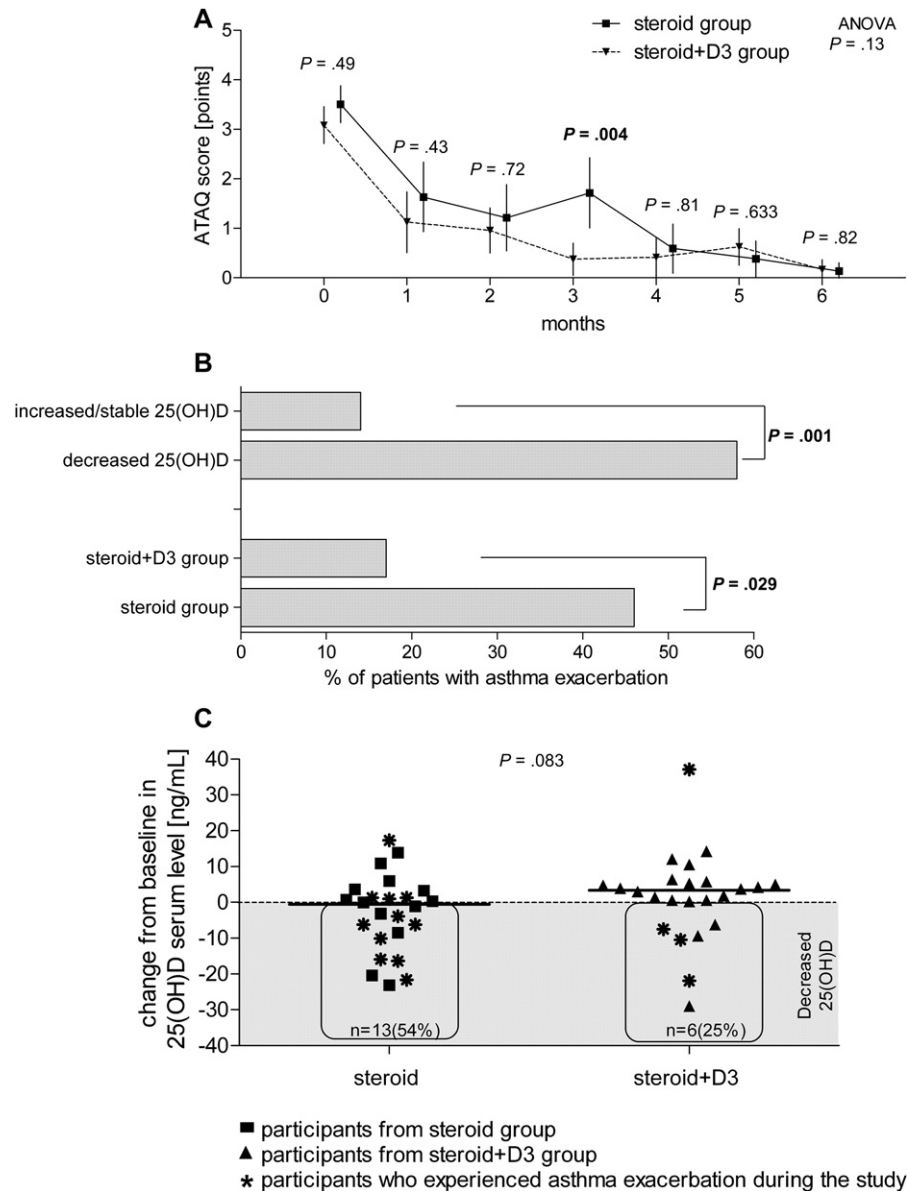


FIG 1. Between-group comparison of changes over time in ATAQ score. Data are presented with means and 95% CIs (*whiskers*) (**A**). Between-group comparisons of incidence of asthma exacerbation (% of patients; **B**) and changes from baseline in serum level of 25(OH)D (ng/mL; **C**). Patients with decreased 25(OH)D were pointed in *boxes*.

supplementation. We observed that vitamin D supplementation in the period from September to July prevented declining serum concentrations of 25(OH)D and reduced the risk of asthma exacerbation triggered by acute respiratory tract infection. Vitamin D, apart from its role in bone and calcium metabolism, is involved in the regulation of innate as well as adoptive immune functions, including the response to respiratory infection.⁵ We suspect that vitamin D boosts the effectiveness of the antimicrobial response of the innate immune system, simultaneously diminishing the natural consequences of inflammation, which appear to have an adverse effect on asthma pathogenesis.⁶ This may explain our results, which deliver new clinical evidence supporting the role of vitamin D in the prevention of asthma exacerbation in children; such findings are in accordance with other studies.⁷ We did not observe smaller clinical improvement in children with a very high 25

(OH)D serum level at baseline. Moreover, the significant increase of 25(OH)D was not associated with a weaker clinical response to antiasthma treatment. Both findings seem important considering the risk of supplementation with vitamin D in children with asthma. On the basis of our results, we can only speculate on the precise mechanism by which vitamin D interferes with immune functions. Therefore, more in-depth studies are needed to explain all aspects of vitamin D activity in asthma. The dose of vitamin D in the current study approximated the dose recommended by the Institute of Medicine, but it was clearly inadequate to increase 25(OH)D serum levels. Interestingly, the children's response varied greatly as well (Fig 1, C), which could be a result of noncompliance or genetic susceptibility. Although the dose of vitamin D was inadequate, significant benefits were achieved in the current study.

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