

The relationship between serum vitamin D level and asthma

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ABSTRACT

OBJECTIVE: Several studies have established a relationship between low serum vitamin D levels and the onset of asthma in childhood. In this study, we aim to assess the relationship between vitamin D and asthma.

METHODS: This study included 29 mild and 30 moderate persistent asthma and 38 healthy control group. Evaluation of the three groups was carried out in respect of serum vitamin D levels, Respiratory Function Test (RFT), and Exercise Provocation Test (EPT). The two asthma groups were also examined using the Asthma Control Test (ACT) and Nitric Oxide in Exhaled Breath (FeNO) level.

RESULTS: The vitamin D levels of the mild and the moderate persistent asthma groups were determined to be lower than the vitamin D levels of the control group ($p=0.007$). A significant negative correlation was determined in all cases between the vitamin D levels and the broncho-reversibility percentage ($p=0.0002$). The negative correlation between the vitamin D levels and the broncho-reversibility percentage was more evident in the moderate persistent asthma group ($p=0.0001$). In the moderate persistent asthma group, a significant positive correlation was determined between the lowness of the maximum forced expiratory volume in EPT and a low vitamin D level ($p=0.009$). The ACT scores were lower, and the FeNO levels were higher in the moderate asthma group compared to the mild asthma group ($p=0.0001$).

CONCLUSION: The findings showed that low serum vitamin D levels were observed more often in children with asthma, and there was a correlation with increased broncho-reversibility in the RFT and increased bronchial hyper-reactivity in the EPT.

Keywords: Asthma; Asthma control test; child; exercise; FeNO; vitamin D.

Cite this article as: Ozkars MY, Keskin O, Almacioglu M, Kucukosmanoglu E, Keskin M, Balci O. The relationship between serum vitamin D level and asthma. *North Clin Istanbul* 2019;6(4):334–340.

In recent years, there has been an increase in both asthma and serum vitamin D deficiency throughout the world in general [1, 2]. This increase has encouraged research on the subject of a relationship between asthma and serum vitamin D deficiency and studies conducted by several researchers have provided valuable contributions to this issue.

In the literature, there is an increasing number of studies related to the therapeutic benefits of vitamin D in patients with asthma. It is noticeable that there is a

relationship between vitamin D deficiency and poorly controlled asthma [3]. It has also been reported that there is a relationship between vitamin D deficiency and increased inflammation in asthma, asthma exacerbation and poorly controlled asthma [4]. Some studies have stated that vitamin D supplementation has reduced severe asthma attacks [5]. Other studies have reported that asthma attacks requiring systemic steroid treatment have reduced with vitamin D supplementation [6].

Received: March 08, 2018 *Accepted:* January 07, 2019 *Online:* July 04, 2019



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In investigations into the relationship between asthma and serum vitamin D deficiency, various methods have been used. One of these methods used is the respiratory function test [1, 2]. Other methods used show the relationship between vitamin D and the exercise provocation test [7, 8] and the measurement of nitric oxide in exhaled breath [7–9]. Researchers have also examined the relationship of the serum vitamin D level with asthma using the Asthma Control Test [10, 11].

This study aims to evaluate the relationship of serum vitamin D levels with mild and moderate persistent asthma in paediatric patients using measurements of broncho-reversibility in the respiratory function test, bronchial hyper-reactivity in the exercise provocation test and nitric oxide in exhaled breath. Thus, through a better understanding of the effects of serum vitamin D levels on asthma, the subject of the necessity for vitamin D supplementation in asthma treatment was discussed.

MATERIALS AND METHODS

Study Design

The study participants were selected from cases presenting at the Paediatric Immunology and Allergy Polyclinic of Gaziantep University Medical Faculty Hospital. The asthma group was formed of newly-diagnosed, treatment-naive cases. That all the asthma patients were not in an exacerbation phase, had no infectious disease, and no other chronic disease was determined from the anamnesis, and the findings of physical examination and laboratory tests. The control group was formed of healthy volunteers who presented at the hospital for various reasons and were determined with no acute or chronic disease and no allergic disease with the ISAAC questionnaire [12]. As a result of the patient selection, three groups were formed of 29 children with mild persistent asthma, 30 children with moderate persistent asthma and 38 healthy control subjects. The subjects ranged in age from 7 to 14 years old. The Ethics Committee of the Gaziantep University Medical Faculty approved this study (Code: 02-2013/76). Informed consent was obtained from each patient who was included in this study, and the study protocol was followed according to the ethical guidelines of the 2014 Declaration of Helsinki.

Laboratory Analysis and Data Collection

On the first day, all the patients with asthma were applied with the fractional exhaled nitric oxide (FeNO/NIOX,

Aerocrine AB, Stockholm, Sweden) measurement and the asthma control test (ACT) questionnaire. The values of FeNO were stratified into: low (<20 ppb for children under 12 years of age and <25 ppb for the children older than 12 years), intermediate levels (20–35 ppb for children under 12 years of age and 35–50 ppb for children above 12 years of age), and high levels (>35 ppb for children under 12 years of age and >50 ppb for those older than 12 years) [13]. Then, the respiratory function test (RFT) was applied to measure broncho-reversibility and full blood count, serum IgE and serum vitamin D tests were made. The following day, the exercise provocation test (EPT) was applied to all the cases.

In this study, broncho-reversibility in the RFT, percentage change in forced expiratory volume (FEV₁ change %), bronchial hyper-reactivity in EPT and the measured maximum forced expiratory volume reduction (max FEV₁ reduction) were examined.

Following the basal measurement of broncho-reversibility [15 mins after inhalation of 400 mcg (4 puffs) salbutamol], the percentage change from the basal value in FEV₁ was recorded (FEV₁ % change in RFT).

Bronchial hyper-reactivity was applied according to the test protocol of the American Thorax Society/European Respiratory Society (ATS/ERS) [14]. After the basal measurement, the FEV₁ change percentages were recorded at 5, 10, 15, 20 and 30 mins after running on a running band for 6 mins by children aged <12 years and 8 mins for those aged ≥12 years to provide 80%–90% of maximum heartbeat rate (220- age). The reductions were recorded as negative values. The highest change % was recorded as the maximum FEV₁ reduction.

Due to the temporary changes caused in FeNO, spirometric procedures were applied after the FeNO measurement. Care was taken that the patients were not obese, that they fasted for one hour before the measurement, the mouth was rinsed with water, they were not exposed to cigarette smoke, and they had not recently had any upper or lower respiratory tract infection.

Statistical Analysis

One-way ANOVA and Independent Samples T-test were used to investigate a possible relationship between FeNO levels and serum vitamin D concentration and serum vitamin D concentration and serum vitamin D concentration. A Pearson Correlation Test analysis was used to investigate the possible association between RFT results and serum vitamin D concentration and EPT re-

TABLE 1. Demographic characteristics of the study participants

| | Mild persistent asthma (n=29) | Moderate persistent asthma (n=30) | Control group (n=38) | p |
|----------------------|----------------------------------|--------------------------------------|-------------------------|--------------------|
| Age (years)* | 11.8±2.7 | 11.0±3.0 | 12.7±2.8 | 0.131 ¹ |
| Gender (female/male) | 13/16 | 13/17 | 20/18 | 0.710 ² |
| Body weight (kg)* | 46.3±3.0 | 41.8±2.9 | 45.8±1.9 | 0.392 ¹ |

*Mean±Standard deviation; ¹One-Way Anova Test; ²Chi-square Test.

TABLE 2. Examination results of the study participants

| | Mild persistent asthma (n=29) | Moderate persistent (n=30) | Control group (n=38) | p |
|--|----------------------------------|-------------------------------|-------------------------|---------------------|
| Eosinophil perecentage (%)* | 5.8±4.1 | 6.3±3.6 | 3.1±3.2 | 0.001 ¹ |
| Vitamin D (ng/mL)* | 17.0±4.8 | 16.4±5.6 | 20.0±4.7 | 0.007 ¹ |
| IgE (IU/ml)* | 299.7±295.1 | 475.8±337.7 | 67.5±60.2 | 0.0001 ¹ |
| Basal FVC (%)* | 96.2±10.5 | 94.0±14.4 | 97.4±1.4 | 0.585 ¹ |
| Basal FEV ₁ (%)* | 96.2±9.7 | 89.4±13.2 | 103.8±12.9 | 0.0001 ¹ |
| Basal FEF ₂₅₋₇₅ (%)* | 61.2±22.9 | 50.6±15.1 | 78.0±23.6 | 0.0001 ¹ |
| Basal FEV ₁ /FVC* | 85.5±8.3 | 82.1±10.2 | 90.5±7.8 | 0.001 ¹ |
| RFT FEV ₁ change (%)* | 7.3±4.7 | 9.6±5.1 | 1.95±2.8 | 0.0001 ¹ |
| EPT maxFEV ₁ reduction (%)* | -5.8±5.2 | -8.2±8.7 | -4.7±3.6 | 0.054 ¹ |
| EPT positive number of patients | 3 (%5.1) | 9 (%15.3) | 0 | 0.003 ¹ |
| FeNO (ppb)* | 23.6±11.0 | 47.9±14.8 | – | 0.0001 ³ |
| FeNO level result | | | | 0.0001 ² |
| Low | 17 | 2 | – | |
| Moderate | 8 | 8 | – | |
| High | 4 | 20 | – | |
| ACT score* | 20.3±2.8 | 14.6±4.2 | – | 0.0001 ³ |
| ACT score result | | | | 0.0001 ² |
| Full control | 19 | 2 | – | |
| Partial control | 10 | 18 | – | |
| Not under control | 0 | 10 | – | |

*Mean±Standard deviation; ¹One-Way Anova Test; ²Chi-square Test; ³Independent Samples T-Test; FVC: Forced Vital Capacity; FEV₁: Forced Expiratory Volume In 1 Second; FEF: Peak Expiratory Flow; RFT: Respiratory function test; EPT: Exercise provocation test; FeNO: Fractional exhaled nitric oxide; ACT: Asthma control test.

sults and serum vitamin D concentration. $P < 0.05$ was considered statistically significant.

RESULTS

The demographic characteristics of the study groups and the control group are summarised in Table 1. The exam-

ination results of the study groups and the control group are shown in Table 2. No statistically significant relationship was determined in the current study between the FEV₁ and FVC values and serum vitamin D levels.

Vitamin D Results

A statistically significant difference was determined

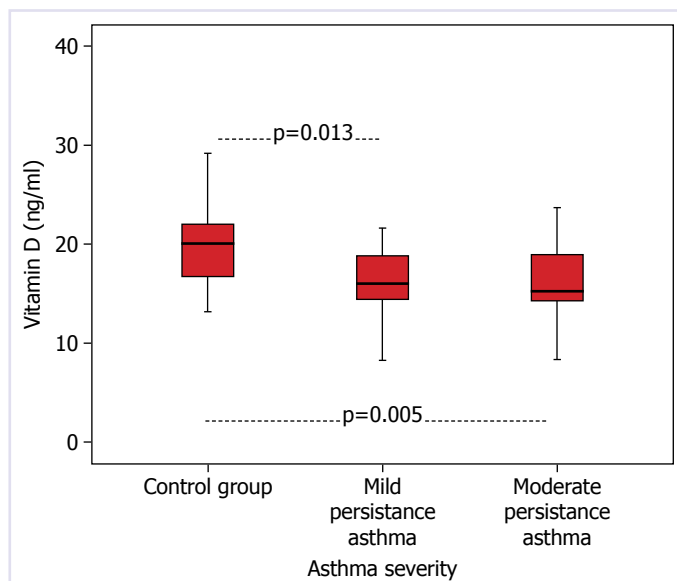


FIGURE 1. Distribution of vitamin D levels according to the severity of asthma.

between the control group and the mild and moderate persistent asthma groups in respect of vitamin D levels ($p=0.007$). The vitamin D levels of the mild persistent asthma group and the moderate persistent asthma group were lower than those of the control group (respectively $p=0.013$, $p=0.005$) (Fig. 1).

RFT Results

In 13 (22.1%) of the asthma patients, the FEV_1 change percentage was $\geq 12\%$. Of these patients, 7 (11.9%) of them were in the mild persistent asthma group, and 6 (10.2%) of them were in the moderate persistent asthma group. In all the cases, a significant negative correlation was determined between the vitamin D levels and the FEV_1 % change (broncho-reversibility) ($p=0.0002$, $r=-0.372$, $n=98$) (Fig. 2A). The negative correlation between the FEV_1 % change and serum vitamin D levels was more evident in the moderate persistent asthma group ($p=0.0001$, $r=-0.623$, $n=30$) (Fig. 2B).

EPT Results

The EPT was positive in 12 (20.7%) of the asthma patients, and 3 (5.1%) of them were in the mild persistent asthma group and 9 (15.3%) of them were in the moderate persistent asthma group.

A significantly positive correlation was determined between the max FEV_1 reduction and serum vitamin D levels in all cases ($p=0.023$, $r=0.231$, $n=98$) (Fig. 2C).

The positive correlation between the maximum FEV_1 reduction in the exercise test and serum vitamin D levels was more evident in the moderate persistent asthma group ($p=0.009$, $r=0.468$, $n=30$) (Fig. 2D).

FeNO Results

The FeNO levels of the asthma patients were determined as low in 19 (32.2%) patients, moderate in 16 (27.1%) patients and high in 24 (40.7%) patients. The FeNO levels of the moderate persistent asthma group (47.9 ± 14.8) were determined to be higher than patients in the mild persistent asthma group (23.6 ± 11.0) ($p=0.0001$) (Fig. 3A).

No correlation was determined between the FeNO levels and the serum vitamin D levels.

ACT Results

According to the ACT results, 19 (32.2%) patients were evaluated as good, 29 (49.2%) as moderate and 11 (18.6%) as poor. The ACT scores of the moderate persistent asthma group (14.6 ± 4.2) were lower than those of the mild persistent asthma group (20.3 ± 2.8) ($p=0.0001$) (Fig. 3B).

No correlation was determined between the ACT scores and the serum vitamin D levels.

DISCUSSION

Several studies have established an association between serum vitamin D levels and asthma incidence [4]. The results of the current study showed that low serum vitamin D levels were observed more frequently in children with asthma. Moreover, a relationship was shown between increased broncho-reversibility in pulmonary functions and increased bronchial hyper-reactivity in the exercise provocation test and serum vitamin D levels.

No statistically significant relationship was determined in the current study between the FEV_1 and FVC values and serum vitamin D levels. In a previous cross-sectional study of adults, a relationship was shown between FEV_1 and FVC values and serum vitamin D levels [15]. However, Tolppanen et al. did not determine a relationship between FEV_1 and FVC values and serum vitamin D levels in a study, including paediatric age groups [16]. There could be two different reasons for these different results. First is that the patients of the current study were children, and the second is that a compatible correlation may not always be seen between the RFT and the symptoms of asthma.

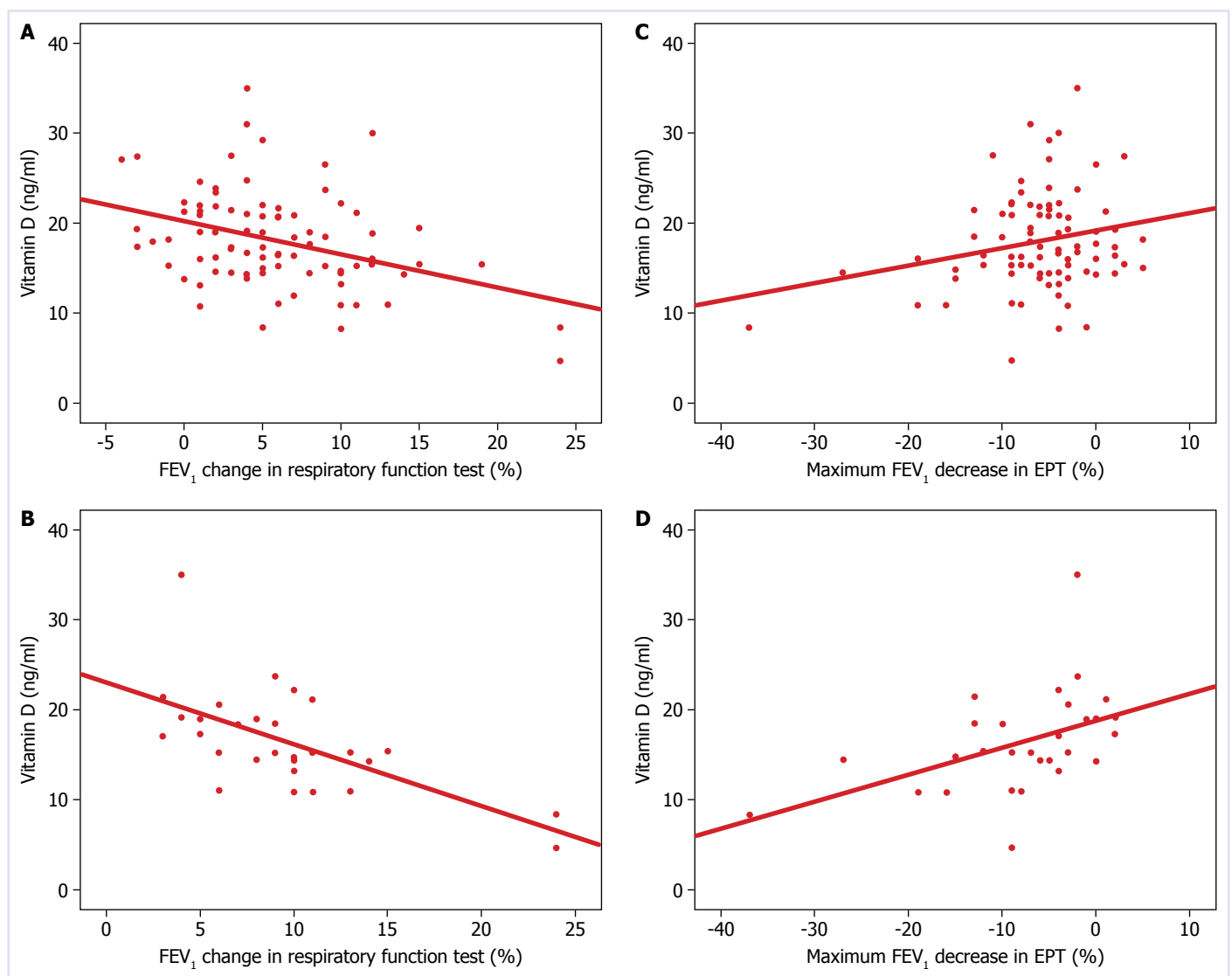


FIGURE 2. The relationship between FEV_1 % change in RFT and vitamin D levels in all cases **(A)**. The relationship between FEV_1 % change in RFT and vitamin D levels in patients with moderate persistent asthma **(B)**. The relationship between maximum FEV_1 reduction in EPT and serum vitamin D levels in all cases **(C)**. The relationship between maximum FEV_1 reduction in EPT and serum vitamin D levels in the moderate persistent asthma group **(D)**.

In the current study, a significantly positive correlation was determined between the reduction in $maxFEV_1$ values and serum vitamin D levels, and this correlation was more evident in the moderate persistent asthma group. A study conducted in asthmatic children in Costa Rica found a relationship between increased airway sensitivity in the methacholine test and serum vitamin D levels [17]. There has not yet been full clarification of the relationship between bronchial hyper-reactivity associated with exercise and low serum vitamin D levels. A previous study determined an increase in the number of mast cells in connective tissues in patients with low serum vitamin

D levels [18]. In another study, vitamin D was reported to increase apoptosis and inhibit the maturation of precursor mast cells of bone marrow origin in mice, and inhibit the expression of histamine from mast cells [19]. Other studies showed that IL-13 expression was reduced by vitamin D analogues [20] and there was a relationship between bronchial hyper-reactivity associated with exercise and IL-13 polymorphism in children with asthma [21]. These studies suggest that the inflammatory mediators in cases giving a response of bronchoconstriction to exercise were of mast cell origin and/or are mediated by IL-13. In addition, many studies showed that the

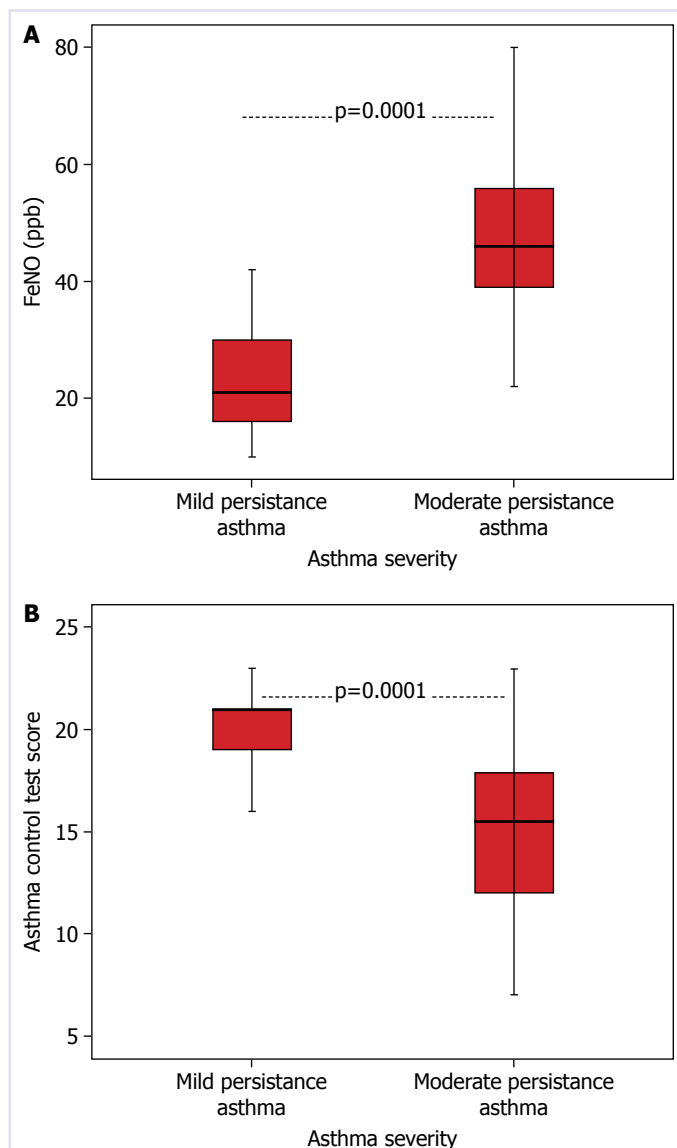


FIGURE 3. Distribution of the FeNO levels according to the severity of asthma **(A)**. Distribution of the ACT scores according to the severity of asthma **(B)**.

primary controller of natural and acquired immunity is vitamin D [22]. The clinical severity of the disease, the number of exacerbations and the systemic glucocorticoid need were related to vitamin D level [23].

The results of the current study showed that the FeNO levels of the moderate persistent asthma group were higher than those of the mild persistent asthma group and no correlation was determined between the FeNo levels and the serum vitamin D levels. Similarly, in a study by Bar et al. [7], no relationship was shown between FeNO and serum vitamin D in asthma. Dabbah et al. [8] also showed no relationship between FeNO and

vitamin D in asthma, and Tenero et al. [9] reported that the administration of vitamin D to asthma patients had no effect on the FeNO levels.

In both asthma groups of the current study, no correlation was determined between the ACT scores and serum vitamin D levels. In a study by Jolliffe et al. [11], no relationship was seen between the ACT scores and serum vitamin D levels. However, Boonpiyathad et al. [10] stated that a correlation was found between vitamin D and ACT. Similarly, Havan et al. [24] also reported a relationship between serum vitamin D levels and ACT.

Due to these noticeably conflicting results in previous studies, there is a clear need for further studies to examine the relationship between vitamin D and asthma.

Conclusions

In conclusion, the results of the current study showed that low serum vitamin D levels were observed more frequently in children with asthma, and there was a relationship between increased broncho-reversibility in RFT and increased bronchial hyper-reactivity in EPT and serum vitamin D levels.

Ethics Committee Approval: Ethics Committee of the Gaziantep University Medical Faculty approved this study (Code: 02-2013/76).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – M.Y.O., O.K., M.A.; Design – M.Y.O., O.K., M.A.; Supervision – O.K., E.K., M.K.; Materials – M.Y.O., O.K., M.A.; Data collection and/or processing – M.Y.O., O.K., M.A., O.B.; Analysis and/or interpretation – M.Y.O., O.K., M.A.; Writing – M.Y.O., O.K., M.A.; Critical review – M.K., E.K.

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