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Original Research Article

Evaluation of vitamin D levels in allergic and non-allergic asthma

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ABSTRACT

Background and objective: Some researches show that low vitamin D may play a role in asthma pathogenesis. The aim of this study was to evaluate the serum vitamin D level in asthmatics with different phenotypes and to determine its associations with lung function, IgE, eosinophil count and body mass index (BMI).

Materials and methods: The study population comprised 85 patients with asthma and 73 healthy persons. Patients with asthma were divided into groups according to phenotypes. Allergy was assessed using a skin prick test and measuring eosinophil count in peripheral blood and total IgE in serum. Lung function was evaluated by spirometry. Concentration of vitamin D (25(OH)D3) was measured using a commercial ELISA kit. Smoking history was assessed and BMI was calculated for all individuals.

Results: The vitamin D level was lower in asthmatics than in the control group (14.36 ± 0.57 vs. 22.13 ± 0.84 ng/mL, $P < 0.001$). There were no significant differences in the vitamin D level between the groups with allergic and non-allergic asthma (14.36 ± 0.77 vs. 14.35 ± 0.74 ng/mL). The low vitamin D level increased the risk of asthma 1.2 times (OR, 1.194; 95% CI, 1.109–1.286, $P < 0.01$). The vitamin D level did not correlate with lung function and markers of allergy in asthmatic patients. The vitamin D level correlated with FEV1/FVC ($rs = 0.72$, $P < 0.05$) in smoking patients with asthma. Correlation between the vitamin D level and BMI was found in all studied subjects ($rs = -0.18$, $P < 0.05$).

Conclusions: The vitamin D level was lower in asthmatic patients than in healthy individuals despite their hypersensitivity and increase risk of asthma. There was no relation between the vitamin D level and lung function, eosinophil count and total IgE level, whereas the lower vitamin D level was associated with higher BMI.

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1. Introduction

Asthma is a chronic inflammatory airway disease, which pathogenesis has not been fully investigated yet. Despite the progress of medical science in asthma field, morbidity of this disease remains high worldwide [1]. A more comprehensive understanding of asthma mechanisms may lead to discover more specific diagnostic methods and ways of treatment and prevention.

It is known that many cells are involved in the development of asthma: mast cells, eosinophils, neutrophils, T lymphocytes, macrophages and epithelial cells [2]. T helper 2 cells (Th2) activates interleukin (IL) 5 and granulocyte macrophage colony-stimulating factor (GM-SCF), which induce angiogenesis, differentiation and chemotaxis of eosinophils, and IL 13, which increases airway remodeling and inflammation [3,4]. However, scientists still discover new cytokines, mediators, proteins and other substances that may be involved in asthma pathogenesis.

Vitamin D is a fat-soluble nutrient, which is the best known as a key factor in bone mineralization [5,6]. Vitamin D3 is converted to 25(OH)D in liver and later 25(OH)D is converted into the active form 1,25(OH)2D in kidneys [6]. Some studies showed that role of vitamin D was wider [7–9]. This nutrient may participate in pathogenesis of oncological, endocrine, cardiovascular, psychiatric, autoimmune and allergic diseases including asthma [10–14]. The role of vitamin D in asthma may be explained by its impact on T cell [3,4,12,15]. It was shown that Th1/Th2 ratio and elevated inflammatory mediators were significantly correlated to 25(OH)D levels [12]. Vitamin D induces a higher level of IL-10, which is known as anti-inflammatory cytokine [15]. Receptors of vitamin D are localized in number of tissues including respiratory epithelial cells and bronchial smooth muscle [16]. Pulmonary vitamin D receptors are important for the conversion of 25(OH)D into 1,25 (OH)D in respiratory epithelial cells, moreover, vitamin D receptors and hydroxylase that metabolizes 1,25(OH)D synthesis are increased in bronchial smooth muscle cells [17,18]. 1,25(OH)D has been shown to have anti-inflammatory effect in many tissues including lung tissue [19]. Moreover, a number of genes related to vitamin D may be involved in asthma pathogenesis: some of genes are associated with asthma and atopy; other genes, only with asthma [20].

We aimed to assess serum vitamin D level in asthmatics with different phenotypes according to their allergic and smoking status, and to evaluate its possible relation to lung function, total IgE, eosinophil count and body mass index (BMI).

2. Materials and methods

2.1. Study population

A total of 158 individuals aged more than 18 years were enrolled into the study. Of them, 85 patients had stable asthma, which was controlled with low and medium doses of inhaled glucocorticoids (diagnosed according to the Global Initiative for Asthma [GINA] recommendations) and 73 were healthy subjects [1]. Subjects with asthma were divided into two groups according to their allergic status: with allergic asthma ($n = 56$) and non-allergic asthma ($n = 29$). Patients with allergic asthma were additionally subdivided into 3 subgroups according to the results of a skin prick test: hypersensitivity to one inhaled allergen, to more than one inhaled allergen, and to mixed allergens (inhaled and food). None of the subjects showed signs of acute respiratory infection at least one month before the study. The exclusion criteria were as follows: any acute or chronic respiratory diseases (except asthma), pregnancy, autoimmune and oncologic diseases.

Subjects were divided according to their smoking history into asthmatic smokers ($n = 11$) who were current smokers and asthmatic never-smokers ($n = 74$). Smoking was assessed in pack-years expressed as the product of tobacco use (in years) and the average number of cigarettes smoked per day/20.

BMI was calculated according to the formula BMI = weight (kg)/height (m^2) for all individuals [21].

The study was approved by the Regional Bioethics Committee at the Lithuanian University of Health Sciences (No. BE-2-31). Subjects gave their informed consent.

2.2. Lung function testing

Lung function was evaluated using a CustovitM pneumotachometric spirometer (Custo Med, Germany). All subjects were asked to avoid the use of short-acting β2-agonists for at least 8 h before the testing. Patients were investigated in a sitting position, and a nose clip was used. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured. FEV1/FVC ratio was calculated. The best value of the three measurements was selected. Normal values were defined according to Quanjer et al. [22].

2.3. Evaluation of allergic sensitization

Allergic sensitization was assessed using the skin prick method of Pepys [23] with standard (glycerin-preserved) allergens (Stallergens, France). Skin prick testing was performed on the forearm with common aeroallergens and food allergens as well as histamine (positive control) and glycerin (negative control). The reaction was measured after 20 min. The reaction was considered as positive if the diameter of the wheal was 3 mm or greater.

2.4. Peripheral blood collection and processing

Blood eosinophil count and serum total IgE were measured in peripheral blood. Peripheral blood was collected by peripheral venipuncture according to the standard procedure. Blood samples were drawn into BA vacutainer K3 EDTA tubes for further enumeration of eosinophils with the ADVIA 120 automated hematology analyzer (Germany) and into serum tubes, stored at room temperature for 30–60 min and centrifuged for 15 min at 4000 rpm. Serum samples were immediately frozen at 70 °C for further analysis.

2.5. Measurements of vitamin D level and IgE

Concentration of vitamin D (25(OH)D3) in serum was measured by the enzyme-linked immunosorbent assay ELISA using

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DIAsource 25OH vitamin D Total ELISA kit (Louvain-la Neuve, Belgium). Blood was collected during October, November and December for all subjects. The detection limit was defined as the apparent concentration two standard deviations below the average OD at zero binding was 1.5 ng/mL. The vitamin D level of 30–150 ng/mL was considered to be sufficient; 0–10 ng/mL, deficient; 10–30 ng/mL, insufficient; and >150 ng/mL, toxic [6]. None of the participants received vitamin D supplementation before the study.

IgE level in serum was also measured using the enzyme-linked immunosorbent assay (ELISA, Bio-Clin-Inc., USA) according to the manufacturer's recommendations.

2.6. Statistical analysis

Statistical analysis was performed using statistical program SPSS 13. Methods of statistical analysis were selected after performance of Kolmogorov–Smirnov test. Consequently, the Mann–Whitney *U* and Kruskal–Wallis *H* tests were applied for comparison of vitamin D level between the following groups: asthmatics and healthy individuals, allergic and non-allergic asthma, smokers and non-smokers, and between subgroups of allergic asthma. *T* test was carried out for comparison of BMI and lung function parameters between smoking asthmatics and non-smoking asthmatics and between allergic and non-allergic asthmatics. The Mann–Whitney *U* test was also used to compare total IgE level and eosinophil count between the above mentioned groups. Methods of correlation (Spearman coefficient) and linear regression analysis were used in order to find associations between vitamin D and spirometry values (FEV_1, FVC and FEV1/FVC), eosinophil count, total IgE level and BMI. Binary logistic regression was used to estimate the likelihood of different factors that may have an impact on the development of asthma. A *P* value of <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of study population

Characteristics of the study population are shown in Table 1. The mean age of the studied subjects did not differ between the asthma group and control groups. However, patients with allergic asthma were slightly younger compared to non-allergic asthmatics (Table 2). Although BMI was higher in asthmatic patients than healthy individuals, this difference was not statistically significant (Table 1). The total IgE level and eosinophil count were found to be significantly higher in allergic asthmatic than non-allergic asthmatic patients. Eosinophil count, total IgE level, lung function, and BMI did not significantly differ between smoking and non-smoking asthmatic patients.

Table 1 – Characteristics of the study population.

Characteristic	Asthma group (N = 85)	Control group (N = 73)
Women/men, *n*	59/26	36/37
Age, years	46.41 ± 1.54	41.90 ± 1.75
BMI, kg/m^2	27.71 ± 0.64	25.61 ± 0.59
Smokers/non-smokers, *n*	11/74	23/50
Positive skin prick test, *n*	56	0

Values are mean ± standard error of the mean unless otherwise indicated.

3.2. Vitamin D level

All studied subjects showed a lower vitamin D level than recommended norms (17.95 ± 0.58 vs. >30 ng/mL). The vitamin D level was found to be significantly lower in asthmatic patients than in healthy individuals (Fig. 1), but it did not differ between allergic and non-allergic asthmatic patients as well as between smokers and non-smokers with asthma (Table 2).

Binary logistic regression analysis showed that the low vitamin D level increases asthma risk almost 1.2 times (OR, 1.194; 95% CI, 1.109–1.286; $P < 0.01$). Age, sex, smoking, and BMI did not have a significant impact on asthma development (Table 3).

3.3. Relationship between Vitamin D, lung function, eosinophil count, total IgE level and BMI

In the asthma group, vitamin D levels did not correlate with lung function (FEV1, FVC and FEV1/FVC), eosinophil count, and total IgE level (Table 4). Similarly, these parameters were not

Table 2 – Characteristics of patients with asthma.

Characteristic	Allergic Asthmatics (N = 56)	Non-allergic asthmatics (N = 29)	Smoking asthmatics (N = 11)	Non-smoking asthmatics (N = 74)
Women/men, *n*	36/20	23/6	6/4	53/21
Age, years	42.48 ± 1.91*	54.00 ± 1.94	41.82 ± 3.18	47.09 ± 1.69
BMI, kg/m^2	27.74 ± 0.87	27.64 ± 0.83	28.12 ± 2.70	27.64 ± 0.61
FVC, %	103.76 ± 2.21	104.36 ± 4.47	107.90 ± 7.34	103.42 ± 2.17
FEV_1, %	93.77 ± 2.57	91.17 ± 4.62	94.55 ± 6.16	92.64 ± 2.50
FEV_1/FVC ratio	0.90 ± 0.03	0.84 ± 0.04	0.80 ± 0.08	0.86 ± 0.22
Eosinophil count, $\times 10^9$/L	5.98 ± 0.58*	4.22 ± 0.61	4.56 ± 1.04	5.50 ± 0.49
Total IgE level, kU/L	464.30 ± 82.48**	120.30 ± 41.88	703.51 ± 291.96	291.60 ± 49.50
Vitamin D level, ng/mL	14.36 ± 0.77	14.35 ± 0.74	14.53 ± 1.95	14.33 ± 0.59

Values are mean ± standard error of the mean unless otherwise indicated.
* $P < 0.05$ compared to non-allergic asthmatics.
** $P < 0.01$ compared to non-allergic asthmatics.

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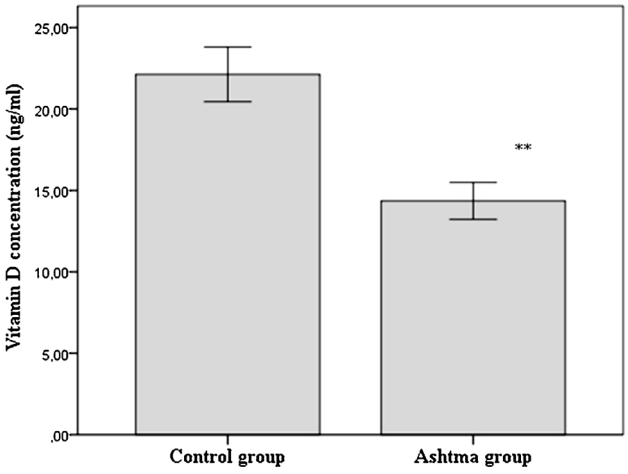

Fig. 1 – Vitamin D concentration in serum from patients with asthma and healthy subjects data are presented as mean ± standard error of the mean. **P < 0.01 compared to the control group.

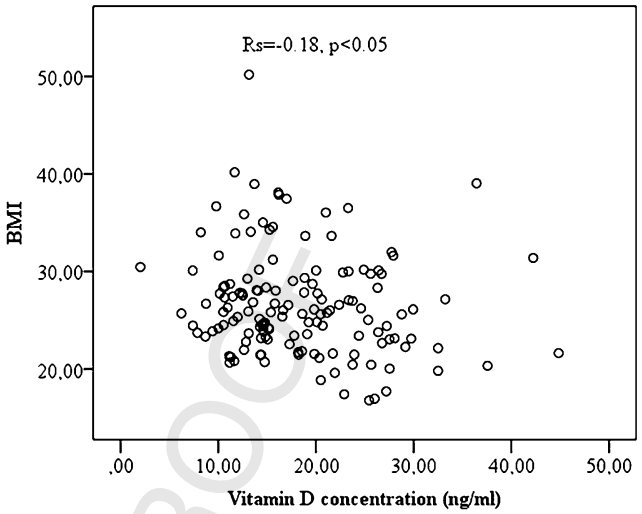

Fig. 2 – Correlation between the vitamin D level and BMI in studied subjects with asthma and healthy subjects.

Table 3 – Evaluation of risk factors for asthma.

Factor	Exp (B)	95% CI for EXP (B)	
		Lower	Upper
Sex	0.402	0.166	0.975
Age	1.002	0.972	1.033
Smoking	0.643	0.221	1.874
Vitamin D level	1.194*	1.109	1.286
BMI	0.931	0.851	1.018

* $P < 0.05$.
$\chi^2 = 49.122$, $P < 0.05$; Hosmer and Lemeshow test 11.747, $P > 0.05$.

associated with vitamin D in separate groups of subjects with allergic and non-allergic asthma. However, vitamin D level negatively correlated with eosinophil count in subgroup of subjects with increased sensitivity to mixed allergen (Table 4). Positive correlation between vitamin D level and FEV1/FVC (rs = 0.72, $P < 0.05$) was estimated in smoking asthmatics.

Negative correlation was found between the vitamin D level and BMI in all studied subjects (Fig. 2). Linear regression confirmed that BMI had an impact on vitamin D level (t = −2.03, $P < 0.05$). No significant relations were estimated between BMI and FEV1, FVC, FEV1/FVC, eosinophil count and total IgE in studied asthmatics.

4. Discussion

Our study reveals that vitamin D level is significantly lower in patients with asthma than healthy subjects and has a link with BMI, but a lack of this vitamin is not related to allergic status of these subjects. We can suggest that lack of vitamin D increases risk of asthma development in 1.2 times. Thereby data from our research suggest that vitamin D may play an important role in pathogenesis of asthma. For the evaluation of vitamin D level, measurement of concentration of 25(OH)D3 has been chosen because it shows a store of vitamin D in the body more accurately than an active form of vitamin D (1,25(OH)2D3) and is metabolized only in the liver by 25-hydroxylase [24]. Whereas 1,25(OH)2D3 is metabolized in the liver and kidneys, and its formation is adjusted by parathormone and calcitonin. Consequently, when analyzing (1,25(OH)2D3) concentration a number of factors that could affect a false level of vitamin D remains. Moreover, blood samples were taken during late

Table 4 – Correlations between the vitamin D level and lung functions, eosinophil count and total IgE in asthma groups (Spearman's coefficient).

Variable	Vitamin D level				
	Allergic asthmatics (N = 56)			Non-allergic asthmatics (N = 29)	Total (N = 85)
	1 inhaled allergen (N = 9)	>1 inhaled allergen (N = 40)	Mixed allergen (N = 7)		
FEV1	0.00	−0.16	0.07	0.07	−0.06
FVC	0.12	−0.05	0.00	0.07	−0.01
FEV1/FVC	0.05	−0.17	−0.36	0.18	0.00
Eosinophil count	0.13	−0.04	−0.79*	−0.15	−0.08

* $P < 0.05$.

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autumn and winter (October, November and December) in order to avoid influence of sun exposure.

There are abundant data about the role of vitamin D in asthma and allergy in recent scientific publications. Our results are in agreement with other studies showing that vitamin D level is decreased in adults and children with asthma [10–14]. In vitro studies show that a lack of vitamin D level reduces secretion of IL-10, which is known as anti-inflammatory cytokine regulating cellular sensitivity to glucocorticoids in lymphocytes and monocytes [15,25–28]. Moreover, a decreased vitamin D level induces secretion of IL-5, IL-6, and IL-8 which are important in pathogenesis of inflammation [26]. Vitamin D also reduces proliferation of airway smooth muscles cells [26]. All these factors can result in the development of asthma or its exacerbation.

On the contrary, other scientists present opposite results showing that a low vitamin D status is not significantly associated with incidence of asthma in most subjects [29–31]. Whereas some of these authors have found that insufficiency of vitamin D is associated only with severe asthma exacerbations [31]. We analyzed those articles which presented no relation between vitamin D level and asthma and noticed that in some studies blood samples were taken in spring and summer and this could lead to a false increase of vitamin D level in asthmatics and healthy subjects.

There is a growing appreciation that asthma is a complex trait caused by multiple environmental factors in combination with different genes, and that it has many different forms or phenotypes [32–34]. Immunologic mechanisms and risk factors for allergic and non-allergic asthma can be quite different, with allergic asthma characterized by eosinophilic inflammation dependent on T helper 2 cells, while non-allergic asthma has neutrophilic inflammation independent of T helper 2 cells [34]. Data from some recent publications show that a low vitamin D level is linked to allergy, especially in children [13,35–38]. This could be explained by impact of vitamin D on T cells and stimulation of secretion of different cytokines which are important in allergic reactions. However, our study did not show a significant link between vitamin D level and allergic status in patients with asthma. Our results are in accordance with some studies showing that a low vitamin D level is associated with non-allergic asthma and severe asthma exacerbations in non-atopic cases [29,31]. The role of vitamin D during non-allergic asthma could be explained only through inflammatory and proliferative mechanisms of airway smooth muscles cells [26].

Eosinophil and IgE are well known components of allergic reactions. Their role in pathogenesis of allergic diseases is well established. Despite that in our study level of eosinophil count in peripheral blood and total IgE in serum was significantly higher in subjects with allergic asthma than in non-allergic asthmatics, we found no correlation between these markers and vitamin D level. However, after division of asthmatics into three subgroups according to the results of the skin prick test, we found an inverse correlation between vitamin D level and eosinophil count in subgroup of patients with hypersensitivity to mixed allergen. It led us to suggest that a lack of vitamin D level becomes significant in pathogenesis of allergic asthma when a patient has allergy to multiple allergens. Controversial data regarding correlation between level of vitamin D and eosinophil count and total IgE are presented in recent studies: some authors show that there is no link between these markers [11,39], while others, present the relation [14,40]. Further studies are required to clarify this hypothesis.

Chronic inflammation negatively influences lung function by increased hyper responsiveness. In vitro studies showed that a lack of vitamin D level can induce proliferation of airway smooth muscle cells through growth factor-induced phosphorylation of retinoblastoma protein and checkpoint kinase 1 [41]. Vitamin D also can influence the growth of these cells by regulation of transcription of genes which are involved in airway remodeling [42]. Some studies show a significant direct relation between vitamin D level and both FEV1 and FEV1/FVC [10,11,25]. In a very recent study performed by Tolppanen et al. a significant associated was found between FEV1 and 25(OH)D2 but no significant correlation between lung function and 25 (OH)D3 which was used in our study [35]. We also found no correlations between vitamin D levels and lung function (FEV1, FVC, FEV1/FVC), however, a positive correlation was noticed between vitamin D level and FEV1/FVC in asthmatic smokers. Lange et al. in their study with healthy smokers have explained the role of vitamin D as protective from smoking induced damaging in airways [43].

It was thought that smoking was linked to a decreased vitamin D level [32,33], but we did not find significant difference of vitamin D level in smokers and non-smokers with asthma. This could be explained by small investigated groups.

According to the literature, adipocytes can accumulate different cytokines and chemokines which are important in pathogenesis of inflammation [44]. Analysis of our study revealed a negative correlation between level of vitamin D and BMI in all studied subjects. Our results are in agreement with data of other authors declaring a lower vitamin D level in obese individuals (both, asthmatics ant healthy persons) and correlation between BMI and vitamin D concentration [25,30,45] The clear explanation why vitamin D level is usually lower in obese people is not known yet. Vimaleswaran et al. have explained high BMI impact on decreased vitamin D level by genetic mechanisms [34]. A recent study performed by Drincic et al. suggested that dilution of ingested or cutaneously synthesized vitamin D in the large fat mass of obese patients explained low vitamin D status [46].

5. Conclusions

The vitamin D level was lower in asthmatic patients than healthy individuals despite their allergic status. Therefore, we argue that a lack of vitamin D is important in the pathogenesis of asthma. However, there was no relation between the vitamin D level and lung function, eosinophil count and total IgE level, whereas the lower vitamin D level was associated with higher BMI.

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Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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REFERENCES

[1] Global Initiative for Asthma (GINA). GINA report, global strategy for asthma management and prevention; 2012, http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf [accessed 23.11.13].
[2] National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR3): Guidelines for the diagnosis and management of asthma – summary 2007. J Allergy Clin Immunol 2007;120(5):S94–138.
[3] Ingram JL, Kraft M. IL-13 in asthma and allergic disease: asthma phenotypes and targeted therapies. J Allergy Clin Immunol 2012;130(4):829–42.
[4] Klein WRG, Kleinjan A, van Nimwegen M, Bergen I, de Bruijn M, Levani Y, et al. Pulmonary innate lymphoid cells are major producers of IL-5 and IL-13 in murine models of allergic asthma. Eur J Immunol 2012;42(5):1106–16.
[5] Ryan JW, Anderson PH, Turner AG, Morris HA. Vitamin D activities and metabolic bone disease. Clin Chim Acta 2013;425:148–52.
[6] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
[7] Brown SD, Calvert HH, Fitzpatrick AM. Vitamin D and asthma. Dermatoendocrinology 2012;4(2):137–45.
[8] Muehleisen B, Gallo RL. Vitamin D in allergic disease: shedding light on a complex problem. J Allergy Clin Immunol 2013;131(2):324–9.
[9] Székely JI, Pataki Á. Effects of vitamin D on immune disorders with special regard to asthma, COPD and autoimmune diseases: a short review. Expert Rev Respir Med 2012;6(6):683–704.
[10] Alyasin S, Momen T, Kashef S, Alipour A, Amin R. The relationship between serum 25 hydroxy vitamin d levels and asthma in children. Allergy Asthma Immunol Res 2011;3(4):251–5.
[11] Li F, Peng M, Jiang L, Sun Q, Zhang K, Lian F, et al. Vitamin D deficiency is associated with decreased lung function in Chinese adults with asthma. Respiration 2011;81(6):469–75.
[12] Maalmi H, Berraïes A, Tangour E, Ammar J, Abid H, Hamzaoui K, et al. The impact of vitamin D deficiency on immune T cells in asthmatic children: a case-control study. J Asthma Allergy 2012;5:11–9.
[13] Ehlayel MS, Bener A, Sabbah A. Is high prevalence of vitamin D deficiency evidence for asthma and allergy risks? Eur Ann Allergy Clin Immunol 2011;43(3):81–8.
[14] Ma XL, Zhen YF. Serum levels of 25-(OH)D(3) and total IgE in children with asthma. Zhongguo Dang Dai Er Ke Za Zhi 2011;13(7):551–3.
[15] Urry Z, Chambers ES, Xystrakis E, Dimeloe S, Richards DF, Gabryšová L, et al. The role of 1α,25-dihydroxyvitamin D3 and cytokines in the promotion of distinct Foxp3+ and IL-10 + CD4+ T cells. Eur J Immunol 2012;42(10):2697–708.
[16] Wittke A, Chang A, Froicu M, Harandi OF, Weaver V, August A, et al. Vitamin D receptor expression by the lung microenvironment is required for maximal induction of lung inflammation. Arch Biochem Biophys 2007;460:306–13.
[17] Hansdottir S, Monick MM, Hinde SL, Lovan N, Look DC, Hunninghake GW. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. J Immunol 2008;181(10):7090–9.
[18] Bosse Y, Maghni K, Hudson TJ. 1alpha, 25-dihydroxy-vitamin D3 stimulation of bronchial smooth muscle cells induces autocrine, contractility, and remodeling processes. Physiol Genomics 2007;29(2):161–8.
[19] Iqbal SF, Freishtat RJ. Mechanism of action of vitamin D in the asthmatic lung. J Investig Med 2011;59(8):1200–2.
[20] Bossé Y, Lemire M, Poon AH, Daley D, He JQ, Sandford A, et al. Asthma and genes encoding components of the vitamin D pathway. Respir Res 2009;10:98.
[21] Tsigos C, Hainer V, Basdevant A, Finer N, Fried M, Mathus-Vliegen E, et al. Obesity management task force of the European association for the study of obesity. Management of obesity in adults: European clinical practice guidelines. Obes Facts 2008;1(2):106–16.
[22] Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European community for steel and coal. Official statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5–40.
[23] Pepys J. Skin testing. Br J Hosp Med 1975;14:412.
[24] Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev 2008;29(6):726–76.
[25] Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. Am J Respir Crit Care Med 2010;181(7):699–704.
[26] Poon AH, Mahboub B, Qutayba Hamid Q. Vitamin D deficiency and severe asthma. Pharmacol Ther 2013;140(2):148–55.
[27] Creed TJ, Lee RW, Newcomb PV, Mambro di AJ, Raju M, Dayan CM. The effects of cytokines on suppression of lymphocyte proliferation by dexamethasone. J Immunol 2009;183:164–71.
[28] Saramaki A, Diermeier S, Kellner R, Laitinen H, Vaisanen S, Carlberg C. Cyclical chromatin looping and transcription factor association on the regulatory regions of the p21 (CDKN1A) gene in response to 1alpha, 25-dihydroxyvitamin D3. J Biol Chem 2009;284:8073–82.
[29] Mai XM, Langhammer A, Camargo Jr CA, Chen Y. Serum 25-hydroxyvitamin D levels and incident asthma in adults: the HUNT Study. Am J Epidemiol 2012;176(12):1169–76.
[30] Menon J, Maranda L, Nwosu BU. Serum 25-hydroxyvitamin D levels do not correlate with asthma severity in a case-controlled study of children and adolescents. J Pediatr Endocrinol Metab 2012;25(7–8):673–9.
[31] Brehm JM, Acosta-Pérez E, Klei L, Roeder K, Barmada M, Boutaoui N, et al. Vitamin D insufficiency and severe asthma exacerbations in Puerto Rican children. Am J Respir Crit Care Med 2012;186(2):140–6.
[32] Zhang Q, Shi LX, Peng NC, Zhuang HJ, Wu DR, Zhang JL. Survey of vitamin D status in 700 healthy adult males in

Guiyang, China. Zhonghua Yi Xue Za Zhi 2012;92(6):397–400.
[33] Cutillas-Marco E, Fuertes-Prosper A, Grant WB, Morales-Suárez-Varela M. Vitamin D deficiency in South Europe: effect of smoking and aging. Photodermatol Photoimmunol Photomed 2012;28(3):159–61.
[34] Vimaleswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, et al. Causal relationship between obesity and vitamin D status: bi-directional mendelian randomization analysis of multiple cohorts. PLOS Med 2013;10(2):e1001383.
[35] Tolppanen AM, Sayers A, Granell R, Fraser WD, Henderson J, Lawlor DA. Prospective association of 25-hydroxyvitamin d3 and d2 with childhood lung function, asthma, wheezing, and flexural dermatitis. Epidemiology 2013;24(2):310–9.
[36] Arshi S, Ghalehbaghi B, Kamrava SK, Aminlou M. Vitamin D serum levels in allergic rhinitis: any difference from normal population? Asia Pac Allergy 2012;2(1):45–8.
[37] Hollams EM, Hart PH, Holt BJ, Serralha M, Parsons F, de Klerk NH, et al. Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study. Eur Respir J 2011;38(6):1320–7.
[38] Akan A, Azkur D, Ginis T, Toyran M, Kaya A, Vezir E, et al. Vitamin D level in children is correlated with severity of atopic dermatitis but only in patients with allergic sensitizations. Pediatr Dermatol 2013;30(3):359–63.
[39] Brehm JM, Celedón JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. Am J Respir Crit Care Med 2009;179(9):765–71.
[40] Sharief S, Jariwala S, Kumar J, Muntner P, Melamed ML. Vitamin D levels and food and environmental allergies in the United States: results from the National Health and Nutrition Examination Survey 2005–2006. J Allergy Clin Immunol 2011;127(5):1195–202.
[41] Damera G, Fogle HW, Lim P, Goncharova EA, Zhao H, Banerjee A, et al. Vitamin D inhibits growth of human airway smooth muscle cells through growth factor-induced phosphorylation of retinoblastoma protein and checkpoint kinase 1. J Pharmacol 2009;158(6):1429–41.
[42] Holgate ST. ADAM metallopeptidase domain 33 (ADAM33): identification and role in airways disease. Drug News Perspect 2010;23:381–7.
[43] Lange NE, Sparrow D, Vokonas P, Litonjua AA. Vitamin D deficiency, smoking, and lung function in the Normative Aging Study. Am J Respir Crit Care Med 2012;186(7):616–21.
[44] Dixit VD. Adipose-immune interactions during obesity and caloric restriction: reciprocal mechanisms regulating immunity and health span. J Leukoc Biol 2008;84(4):882–92.
[45] Song WJ, Kim SH, Lim S, Park YJ, Kim MH, Lee SM, et al. Association between obesity and asthma in the elderly population: potential roles of abdominal subcutaneous adiposity and sarcopenia. Ann Allergy Asthma Immunol 2012;109(4):243–8.
[46] Drincic AT, Armas LA, Van Diest EE, Heaney RP. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. Obesity (Silver Spring) 2012;20:1444–8.

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