The course of bronchial asthma associated with metabolic syndrome in children with different phenotypes depending on vitamin D₃ level

T. L. Protsiuk¹, Ye. V. Herasymova¹, L. O. Protsiuk¹, N. M. Surkova²

¹National Pirogov Memorial Medical University, Vinnytsia, Ukraine, ²Vinnytsia Regional Children’s Clinical Hospital, Ukraine

Key words: asthma, metabolic syndrome, children, vitamin D₃.

Objective: to establish specific features of BA course in children with various phenotypes on the background of metabolic syndrome, depending on serum vitamin D₃ level.

Subjects and methods. 106 children with BA participated in the study. 42 patients had BA associated with metabolic syndrome (MS), and 64 had BA with no MS. By the phenotype 61 (57.5 %) of patients had allergen-induced (allergic) asthma and 45 (42.5 %) – virus-induced (non-allergic) BA. The control group consisted of 44 children (the patients with MS and those without MS and BA), average age 15.5 ± 1.3 years. All the patients underwent a unified complex of diagnostic investigations: general physical examination, measurement of waist circumference and body mass index (BMI), clinical blood test, spirometry, lipid profile. Weight categories (normal weight, excess weight and obesity) were determined by percentiles (P) of BMI variation series with regard to age, as indicated in WHO recommendations. Serum 25(OH)D levels were determined by enzyme immunoassay. Vitamin D level ≥20 ng/ml was considered sufficient, 11–20 ng/ml – insufficient, ≤10 ng/ml – deficient. General and specific serum IgE levels were determined by enzyme immunoassay. The data obtained were processed with Statistica 8 program, P values of less than 0.05 were considered to indicate statistical significance.

Results. In the group of patients with vitamin D₃ level below 20 ng/ml, 19.5 % had controlled BA and 41.3 % – uncontrolled BA, while among the children with vitamin D₃ level over 20 ng/ml, 30.4 % had controlled BA and 8.6 % – uncontrolled BA (χ² = 9.12, P < 0.05). Mean value of vitamin D₃ concentration in the control group was significantly higher than in the patients with BA associated with MS and BA without MS (P < 0.05). The relationship between OW, obesity and atopy was confirmed by high serum level of sIgE antibodies in those weight categories. High sIgE levels to allergens from the pollen of meadow grass, weeds and trees, animal epithelium, household dust mite, food and fungal allergens were determined much more frequently in the children with OW and obesity than in those with NW. In the patients with BA associated with MS and vitamin D₃ level below 20 ng/ml, FEV₁ and FVLC values appeared to be significantly lower as compared to those with vitamin D₃ level over 20 ng/ml (P = 0.002). Inverse relationship between the most important parameters of external respiration function and BMI was established: VLC (rₓ = -0.45, P = 0.002), FVLC (rₓ = -0.52, P = 0.001), FEV₁ (rₓ = -0.78, P = 0.001), respectively.

Conclusions. The severity of BA as well as the degree of its control in the patients with different phenotypes was found to be influenced by both the presence of MS and vitamin D₃ level. Therefore, vitamin D deficiency can be one of the risk factors of BA and MS development, and can affect the severity of both BA and MS course. Vitamin D deficiency and the presence of MS greatly influence FEV₁, FVLC, PEF values, decreasing the indices of external respiration in children and leading to more severe obstruction.
Bronchial asthma (BA) is currently the most prevalent chronic disease in pediatric patients. For more than a century, clinicians have attempted to subdivide asthma into different phenotypes based on triggers that cause asthma attacks, the course of the disease, or the prognosis.

Asthma is a heterogenous disorder that can be classified into several different phenotypes based on triggers that cause asthma attacks, the course of the disease, or the prognosis. Observational studies have demonstrated that asthma among the obese has a clinical presentation that substantially overlap between the 2 groups. Virus-induced asthma is a phenotype which is characterized by a sudden onset and sometimes a severe clinical course. Each viral infection may alter the course of preexisting asthma, or can affect the immune system and subsequently modify the susceptibility to allergen sensitization and asthma in childhood.

Recent cluster analyses have identified an “obese-asthma” phenotype which is characterized by late onset and lack of atopy. In addition, obesity among early-onset asthmatics clearly exists and heightens the clinical presentation. Observational studies have demonstrated that asthma among the obese has a clinical presentation that is more severe, harder to control, and is not as responsive to standard controller therapies [2].

Along with such classic risk factors for BA development as sex, age, family allergic anamnesis, atopy manifestations, eosinophilia, increased body mass index (BMI), there are several factors which can influence the severity of BA, vitamin D3 deficiency being one of them. The study of potential effect of vitamin D3 deficiency on BA course is of great significance because of its ability to influence the cellular and humoral immunity, thus decreasing the inflammatory process [3], as well as due to the predisposition to frequent respiratory diseases in

**Original research**
case of its deficiency. This mechanism is caused by gene expression and cytokine synthesis. A great number of scientific studies demonstrate the relationship between vitamin D₃ level and frequency and severity of viral, bacterial and fungal infection course. Besides, negative correlation was found between infectious process activity, the number of complications and vitamin D₃ level. The major mechanism of vitamin D₃ anti-infectious action is its ability to induce the formation of β-defensin-2 and cathelicidin in macrophages, neutrophils, natural killers (NK-cells) and epithelial cells, destroying microorganisms and being active to bacteria, viruses and fungi. Sufficient level of 25(OH)D₃ supply is associated with increased number of circulating Th1-cells which induce the secretion of anti-inflammatory cytokines (γ-interferon, IL-2, IL-12, TNF-α), while decreased serum 25(OH)D₃ level is followed by activation of Th2-immune response, i.e. by the increase in IL-4, IL-5, IL-13 populations, promotingatomic reactivity of the body. Besides, overweight and obesity were recently found to be caused by low vitamin D₃ level [4], in part, due to high similarity of calcitriol and vitamin D₃ receptor. Vitamin D₃ receptors and vitamin D metabolic enzymes were found in many cells: T- and B-lymphocytes, macrophages, including lung alveolocytes and bronchial smooth muscles [5]. Asthma-related morbidity is higher among children with vitamin D₃ deficiency and obesity, morbidities that frequently co-exist among minority children. However, the effect of co-existent obesity and vitamin D₃ deficiency on pulmonary function is poorly understood [6].

Though many reports on the problem discussed have already been published, the molecular mechanisms of non-classic action of vitamin D₃ are still unstudied. This can be explained by insufficient number of randomized studies to assess the impact of vitamin D₃ on metabolic processes and BA course.

Objective
To establish specific features of BA course in children with various phenotypes on the background of metabolic syndrome, depending on serum vitamin D₃ level.

Materials and methods
106 children with BA (age – 15.8 ± 1.8 years, BMI = 10.2 ± 0.57 kg/m²) participated in the study. By the phenotype 61 (57.5%) of patients had allergen-induced (allergic) asthma and 45 (42.5%) – virus-induced (non-allergic) BA. 42 patients had BA associated with metabolic syndrome (MS), and 64 had BA with no MS. The control group consisted of 44 children (the patients with MS and those without MS and BA), average age 15.5 ± 1.3 years. BA severity, the phenotype, the level of BA control were evaluated by GINA 2011 criteria and “Protocol of diagnosis and treatment of bronchial asthma in children”, approved by the Order of the Ministry of Health of Ukraine of October 8, 2013”.

All the patients underwent a unified complex of diagnostic investigations; general physical examination, measurement of waist circumference and body mass index (BMI), clinical blood test, spirometry, lipid profile. Weight categories (normal weight, excess weight and obesity) were determined by percentiles (P) of BMI variation series with regard to age, as indicated in WHO recommendations (“Classification of BMI in children and adolescents”). In accordance with this classification, the children with BMI corresponding to P5 of variation series, were referred to under-normal weight category; those with BMI corresponding to P5-P84 – to normal weight group; P85-P94 – to excess weight group, and over P94 – to obesity group. Serum 25(OH)D₃ levels were determined by enzyme immunoassay. Blood sampling was done in winter period. In accordance with the recommendations of the US Institute of Medicine, vitamin D₃ level >20 ng/ml was considered sufficient, 11–20 ng/ml – insufficient, ≤10 ng/ml – deficient. General and specific serum IgE levels were determined by enzyme immunoassay. All the analysis were done from 9 to 11 a.m.

Statistical data processing was done with Statistical package for Windows v. 8.0 (№ AXXR910A374605FA) using parametric methods. The normal distribution was evaluated according to Shapiro–Wilk test. Digital information of all clinical investigations was processed by variance statistical method calculating the mean value (M) and its error (m). The comparison of quality indicators was performed using the χ² criterion. The conjugacy coefficient (φ) was determined to estimate the strength of the relationship between the features. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were used to compare the quantitative indices of the two characteristics. The significance of difference between two means was calculated by Student’s t-test (t). Correlation analysis with calculation of Pearson’s correlation (r) was used to establish the relationship between the studied indices. Differences were considered significant if significance value was 95% (P < 0.05).

Results and discussion
Intermittent, mild, moderate and severe BA were diagnosed in 13 %, 39 %, 39 % and 9 % of patients, respectively, by physical and instrumental examination. By etiology 39 % of patients had allergic, 26 % – mixed and 35 % – non-allergic BA. In 50 % of patients BA was controlled and in 50 % – uncontrolled. All the patients were divided into three weight categories by BMI: those with normal weight (NW) – 34.1 %, overweight (OW) – 34.6 % and obesity – 31.3 % of children.

Having grouped all the children according to their weight and age, we found an increased number of children with obesity in pubertal age (OR = 3.6; 95 % CI: 1.14–11.35; P = 0.003; OR = 9.0; 95% CI: 1.56–51.87; P = 0.008 and OR = 3.71; 95 % CI: 1.06–12.98; P = 0.04, respectively). And the number of obese children decreased together with the increase of age (OR = 0.28; 95 % CI: 0.09–0.88; P = 0.003; OR = 0.11; 95 % CI: 0.02– 0.63; P = 0.008; OR = 0.27; 95 % CI: 0.08–0.94; P = 0.04, respectively). No relationship between obesity and sex in BA children were found, but a tendency to increased obesity in males as compared to females (P = 0.059) was observed. Besides, the relationship between body weight and clinical manifestations of allergy was found. Among the children suffering from atopic BA, 37.4 % had excess weight, 34.3 % – obesity, 28.3 % – normal weight, while
among those with mixed BA overweight was found in 25 %, obesity – in 20.8 %, and normal weight – in 54.2 % of patients. More than a half of the patients with non-atopic BA (58.7 %) had normal body weight. The children with atopic BA were found to have overweight (OR = 2.86; 95 % CI: 1.31–6.25; P = 0.005) and obesity (OR = 3.15; 95 % CI: 1.38–7.20 P = 0.007) significantly more often as compared to the patients with non-atopic BA.

In the group of patients with BA associated with MS as well as those with BA without MS there were 32 % of children with vitamin D insufficiency, 42 % – with vitamin D deficiency, and 26 % – with sufficient level of Vitamin D. In the control group there were 33 % of patients with vitamin D deficiency, 9 % – with vitamin D insufficiency, and 58 % – with sufficient vitamin D level. Vitamin D level was largely influenced by the severity of BA. It was 19.8 ± 5.0 ng/ml in intermittent, 17.3 ± 5.9 ng/ml – in mild; 14.9 ± 4.2 ng/ml – in moderate; 12.8 ± 4.6 ng/ml – in severe BA; P < 0.05.

The level of BA control and comorbidity were influenced by the level of vitamin D as well. In the group of patients with BA associated with MS as well as in those with BA and no MS vitamin D level was significantly lower in the children with uncomplicated BA (P = 0.005). It was 18.9 ± 4.9 ng/ml in the group of patients with controlled BA and 12.6 ± 2.7 ng/ml – in those with uncontrolled BA (t = 3.2, P = 0.005).

The patients with vitamin D deficiency were found to have uncontrolled BA four times as often as the children with normal levels of vitamin D. In the group of patients with vitamin D level below 20 ng/ml, 19.5 % had controlled BA and 41.3 % – uncontrolled BA, while among the children with vitamin D level over 20 ng/ml, 30.4 % had controlled BA and 8.6 % – uncontrolled BA (χ² = 9.12, P < 0.05). Mean value of vitamin D concentration in the control group was significantly higher than in the patients with BA associated with MS and BA without MS (P < 0.05). BMI in the patients with vitamin D level below 20 ng/ml was found to be significantly higher than among the children with vitamin D level over 20 ng/ml. Mean value of BMI in the patients with vitamin D level below 20 ng/ml was 32.8 ± 3.4 while among the children with vitamin D level over 20 ng/ml it was 29.01 ± 5.1 (t = 2.49, P = 0.01), respectively. E. Forno, J. C. Celedón [7] found that obesity increases the risk of asthma – and worsens asthma severity or control – via multiple mechanisms. “Obese asthma” is a complex, multifactorial phenotype in children.

Significant increase in triglycerides and cholesterol levels was revealed in the patients with BA together with the decrease of vitamin D level (P < 0.05). There was negative correlation between the level of low density lipoproteins and vitamin D level (r = -0.58, P = 0.008), while the level of high density lipoproteins increased together with the increase of vitamin D level (P = 0.06). No statistically significant differences between the levels of vitamin D and total IgE were found (P > 0.05). Having analyzed immunologic indices, high level of total IgE was revealed practically in all the children with allergic and mixed BA, ranging from 300 to 600 IU/ml, and reaching 1500–2000 IU/ml in some patients. Statistical analysis showed obese children to have higher total IgE level (2.7; 95 % CI: 2.64–2.84) as compared to those with OW (2.46; 95 % CI: 2.40–2.60) and NW (2.37; 95 % CI: 2.30–2.50). Study of the relationship between IgE level and body weight demonstrated that the children with OW not always had high total IgE level (OR = 1.86; 95 % CI: 0.70–5.09, P = 0.21) as compared to the children with NW, while obese children appeared to have higher total IgE level (OR = 4.20; 95 % CI: 1.13–15.60, P = 0.02) than those with normal weight. With high probability (P = 0.02) of correlation (χ² = 4.56) between body weight and total IgE level, strong degree of this association (ρ = 0.59) was found as well. The relationship between OW, obesity and atopy was confirmed by high serum level of sIgE antibodies in those weight categories. High sIgE levels to allergens from the pollen of meadow grass, weeds and trees, animal epithelium, household dust mite, food and fungal allergens were determined much more frequently in the children with OW and obesity than in those with NW. The proportion of patients with NW, OW and obesity having sIgE to meadow grass pollen was 51.7 %, 60.2 % and 84.9 % respectively; to weeds – 50.3 %, 78.6 %, 85.7 %, respectively; to trees – 25.8 %, 43.7 %, 70.8 %, respectively; to epidermal allergens – 56.5 %, 72.8 %, 82.3 %, respectively; and to food allergens – 50.6 %, 55.7 %, 59.8 %, respectively. Besides, obesity in BA children was associated with sensitization to considerably greater number of allergens, namely: to allergens from the pollen of meadow grass (OR = 6.10; 95 % CI: 1.78–3.57; P = 0.0001), weeds (OR = 5.0; 95 % CI: 1.43–8.53; P = 0.006), trees (OR = 4.56; 95 % CI: 1.72–10.0; P = 0.004), animal epithelium allergens (OR = 4.58; 95 % CI: 1.34–7.25. P = 0.003), food (OR = 4.00; 95 % CI: 1.02–6.86; P = 0.004), household dust mite allergens (OR = 3.68; 95 % CI: 1.18–7.08; P = 0.001) and fungus (OR = 2.15; 95 % CI: 1.39–5.39; P = 0.002).

Significant decrease of forced expiratory volume in 1 second (FEV1) and forced vital lung capacity (FVLC), peak expiratory flow rate (PEF) were detected in BA patients as compared to normal values (P = 0.01 and P < 0.001, respectively). FEV1 decrease by 0.49 % (95 % CI: 0.69–0.15), FVLC – by 0.38 % (95 % CI: 0.56–0.14), and PEF – by 0.42 % (95 % CI: 0.42–0.17) with every unit of BMI increase were revealed in the patients with BA associated with MS. Besides, significant decrease of FEV1 values was demonstrated to be influenced by vitamin D level. In the patients with BA associated with MS and vitamin D level below 20 ng/ml, FEV1 and FVLC values appeared to be significantly lower as compared to those with vitamin D level over 20 ng/ml (P = 0.002). Mean value of vitamin D concentration in the control group was significantly higher than among the patients with BA associated with MS and BA without MS (P = 0.003). Inverse relationship between the most important parameters of external respiration function and BMI was established: VLC (r = -0.45, P = 0.002), FVLC (r = -0.52, P = 0.001), FEV1 (r = -0.78, P = 0.001), respectively.

L. A. Lautenbacher et al. [6] found that vitamin D deficiency was associated with pulmonary function deficits among obese children, but not among normal-weight children with asthma, an association that was independent of Th1 and Th2 serum inflammatory measures. Vitamin D deficiency may be one potential mechanism underlying the obese-asthma phenotype.
Conclusions

1. The severity of BA as well as the degree of its control in the patients with different phenotypes was found to be influenced by both the presence of MS and vitamin D₃ level. Therefore, vitamin D₃ deficiency can be one of the risk factors of BA and MS development, and can affect the severity of both BA and MS course.

2. Vitamin D₃ deficiency and the presence of MS greatly influence FEV1, FVLC, PEF values, decreasing the indices of external respiration in children and leading to more severe obstruction.

The perspectives of further scientific research in this direction are to study the best ways of pharmacological therapy and rehabilitation in patients with BA.

Conflicts of Interest: authors have no conflict of interest to declare.

Information about authors:
Protsiuk T. L., MD, PhD, DSc, Associate Professor of the Department of Pediatrics № 1, National Pirogov Memorial Medical University, Vinnytsia, Ukraine.
Herasymova O. V., MD, PhD, Assistant of the Department of Pediatrics №1, National Pirogov Memorial Medical University, Vinnytsia, Ukraine.
Protsiuk L. O., MD, PhD, Assistant of the Department of Hygiene and Ecology, National Pirogov Memorial Medical University, Vinnytsia, Ukraine.
Surkova N. M., Allergist, Vinnytsia Regional Children’s Clinical Hospital, Ukraine.

Відомості про авторів:
Процюк Т. Л., д-р мед. наук, доцент каф. педіатрії № 1, Вінницький національний медичний університет імені М. І. Пирогова, Україна.
Герасимова О. В., канд. мед. наук, асистент каф. педіатрії № 1, Вінницький національний медичний університет імені М. І. Пирогова, Україна.
Процюк Л. О., канд. мед. наук, асистент каф. загальної гігієни та екології, Вінницький національний медичний університет імені М. І. Пирогова, Україна.
Суркова Н. М., лікар-алерголог, Вінницька обласна дитяча клінічна лікарня, Україна.

Сведения об авторах:
Процюк Т. Л., д-р мед. наук, доцент каф. педиатрии № 1, Винницкий национальный медицинский университет имени Н. И. Пирогова, Украина.
Герасимова Е. В., канд. мед. наук, ассистент каф. педиатрии № 1, Винницкий национальный медицинский университет имени Н. И. Пирогова, Украина.
Процюк Л. А., канд. мед. наук, ассистент каф. общей гигиены и экологии, Винницкий национальный медицинский университет имени Н. И. Пирогова, Украина.
Суркова Н. М., врач-аллерголог, Винницкая областная детская клиническая больница, Украина.

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