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COMPARATIVE CHARACTERISTICS OF THE CONDITION OF TISSUE UPPER RESPIRATORY TRACT IN CHILDREN WITH RESPIRATORY DISEASES LIVING IN KYRGYZSTAN, LOCATED AT DIFFERENT ALTITUDES ABOVE SEA LEVEL

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Abstract

The respiratory tract acts as a crucial barrier influenced by environmental factors, particularly affecting the homeostasis of its mucous membranes. Environmental conditions, including climate and atmospheric composition, play a significant role in the development and progression of respiratory diseases such as bronchial asthma and allergic rhinitis. Various risk factors, including genetic predisposition, viral infections, allergen exposure, and pollutants, along with changes in the microbiome, are key determinants in the manifestation and progression of these diseases. Certain pollutants like ozone (O3), nitrogen dioxide (NO2), and particulate matter (PM2.5) contribute to airway inflammation and hyperresponsiveness, potentially leading to increased oxidative stress and respiratory distress.

This study aims to comparatively analyze the clinical characteristics and processes of free radical oxidation in the tissues of the respiratory tract of children with respiratory diseases living at different altitudes in Kyrgyzstan.

A total of 209 children, including 104 with chronic respiratory diseases and 105 healthy controls, were examined. The study included clinical examinations, endoscopic evaluations, and biopsies when necessary. Biological samples such as exhaled air condensate and nasal lavages were collected to measure various biochemical indicators including total lipids, hydroperoxides, diene conjugates, and oxidative index. Preliminary results indicate that children residing at higher altitudes exhibit more pronounced changes in respiratory tissues, likely due to climatic and environmental factors specific to high-altitude regions. These children showed significantly higher levels of free radical oxidation products and altered surface tension in biological samples compared to those living at lower altitudes. Complaints such as shortness of breath, difficulty breathing, cough, and nasal congestion were also more frequent among children at higher altitudes.

The study highlights the need for further research to better understand the impact of altitude on respiratory health and to develop effective strategies for the treatment and prevention of respiratory diseases in children.

Future research should focus on the longitudinal tracking of respiratory health, detailed environmental assessments, and the development of targeted public health strategies to address the unique challenges faced by high-altitude populations.

Ultimately, this research aims to improve respiratory health outcomes for children living in diverse geographic settings.

Keywords: *surfactant, bronchial asthma, pathogenesis, immunomodulation, endonasal swabs, pathophysiology.*

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Introduction

The respiratory tract is one of the barriers that are influenced by the environment, primarily by influencing the homeostasis of the mucous membranes of the respiratory tract [*Agache I et al., 2019; Tikhonova I et al., 2020; Suhaimi N et al., 2022; Wuyam B et al., 2022*]. At the same time, the most important role in disorders of the respiratory system and the development of bronchial asthma and allergic rhinitis is played by climate features and the composition of the atmosphere of urban housing [*Tikhonova I et al., 2020; Wuyam B et al., 2022*].

An important determinant of the development and progression of the disease at its various stages are multiple risk factors, in particular, genetic predisposition, the presence of a viral infection, contact with allergens or pollutants, and changes in the microbiome [*Siroux V, Bouzigon E, 2019; Altman M et al., 2020; Lukacs N, Huang Y, 2020; Bebic Z et al., 2022*].

Inflammation in the airways can be caused by certain pollutants (O3, NO2, PM2.5), and it has been shown that airway hyperresponsiveness is likely caused by exposure to O3 and NO2 [*Johannson K et al., 2015; Kravchenko J, Lyerly H, 2018; Sierra-Vargas M et al., 2023*]. It has been established that at high concentrations, air pollutants have a direct inflammatory effect on the neuroreceptors of the respiratory tract and on epithelial cells. In addition, various substances present in the atmosphere (O3, NO2, and PM2.5) contribute to increased oxidative stress [*Johannson K et al., 2015; Bebic Z et al., 2022*].

A number of studies have shown that the uncontrolled formation of reactive oxygen species plays an important role in the pathogenesis of a number of pathological processes at the cellular level. Oxidation of a number of molecules leads to unregulated and premature activation of signaling pathways, which causes the development and progression of diseases, including diseases of the respiratory system [*Kravchenko J, Lyerly H, 2018; Altman M et al., 2020; Liu K, Hua S, Song L, 2022; Sierra-Vargas M et al., 2023; Tran H et al., 2023*].

Oxidative stress has been shown to play a crucial role in the pathogenesis of bronchial asthma. The accumulation of reactive oxygen species can contribute to the development and maintenance of inflammatory processes in the respiratory tract, and it is assumed that increased reactive oxygen species production occurs after the development of inflammation under the influence of so-called post-asthmatic triggers and the development of disease attacks [*Shahpoury P et al., 2021*].

The complexity of the pathogenesis of bronchial asthma and the instability of response to treatment also indicate the need for further research to clarify the pathogenesis and search for new therapeutic targets for this disease. One of the promising directions for studying the pathogenesis of asthma is currently analyzing the role of surfactant, changes in the state of which are considered in aspects of pathogenesis, diagnosis of the disease, and also as a potential therapeutic target.

At the same time, reports on the pathogenetic role of free radical oxidation processes and disorders of the antioxidant system state in pathology of the lungs and upper respiratory tract are not systematized. This fully applies to assessing the characteristics of these processes in children depending on their residence at different altitudes above sea level. There are no data of this kind in the available literature.

Goal of the work – a comparative study of clinical characteristics and processes of free radical oxidation in the tissues of the respiratory tract of children with respiratory diseases living at different altitudes above sea level.

Material and methods

Study design and population: At the Osh Interregional Children's Clinical Hospital, the Department of Pulmonology examined 209 children - residents of different regions of Kyrgyzstan, including 104 children with chronic respiratory diseases (57 boys and 47 girls) and 105 healthy children (48 boys and 56 girls).

Inclusion and Exclusion criteria:

Inclusion Criteria:

- Children aged [7-14 years].
- Diagnosed with respiratory diseases (e.g., asthma, bronchitis, pneumonia).
- Residents of Kyrgyzstan.
- Available medical records and consent for participation.

Exclusion Criteria:

- Children with congenital respiratory conditions.
- History of chronic systemic diseases affecting the respiratory tract.
- Recent upper respiratory tract infections (within the last month).
- History of recent surgery or trauma to the respiratory tract.
- Children on immunosuppressive therapy.
- Inability to provide consent or participate in the study.

Study protocol and measurements: The examined children were included into 3 groups depending on their residence in areas located at different altitudes above sea level: 72 children living in Osh (880 *m* above sea level), included in 2 groups: group 1A (control) - 38 healthy children; group 2A (main) - 34 children with respiratory diseases (protracted bronchitis and bronchial asthma); 75 children living in the village Gulcho (Alay region) (1400 *m* above sea level), included in 2 groups: group 1B (control) - 35 healthy children; group 2B (main) - 40 children with respiratory diseases (protracted bronchitis and bronchial asthma);62 children living in the village Daroot-Korgon of Chong-Alay region (3000 *m* above sea level), included in 2 groups: group 1B (control); and 32 healthy children; group 2B (main) - 30 children with respiratory diseases (protracted bronchitis and bronchial asthma). In children included in the study, exhaled air condensate was collected using the method of Belov G.V. and co-authors [*Belov G et al., 2005; Dobryh V, Mun I, 2005*], as well as nasal lavages using the generally accepted method. In these biological media, surface tension indicators were determined, as well as the concentrations of a number of substances and indicators: the levels of total lipids, hydroperoxides, diene conjugates, and the oxidative index was assessed. Determination of surface activity of endonasal swabs and exhaled air condensate (EAC) on a TSM-001 tensiospectrometer, spectrophotometric determination of lipid peroxidation products, catalase in endonasal swabs and EAC. Endonasal washes were obtained by injecting alternately into one nostril and suctioning saline solution from the other nostril using medical vacuum suction. Children were given 100 *ml* of saline. The study was carried out in the first portion of washing water (20 *ml*), since in some cases saline solution with the addition of drugs was then used. Exhaled air condensate was received in the morning on an empty stomach under basal metabolic conditions, a chemically clean glass flask was placed in a container with ice, and the child exhaled air into it through a mouthpiece and connecting tube for 10 *minutes*, without forcing breathing, and 2-5 *ml* of condensate was collected.

Statistical analysis: Statistical data processing was carried out using the STATISTICA 10.0 software package. For comparative analysis of values in groups, the nonparametric Mann-Whitney rank test was used for quantitative parameters (taking into account the nonparametric distribution and high difference in variances in the groups) and the chi-square test for categorical variables. When p-value <0.05, the results were assessed as statistically significant.

RESULTS

The age of the children in groups 1A and 2A was13.3±2.5 years, in groups 1B and 2B - 13.6±1.7 years, in groups 1B and 2B - 12.9±2.4 years. The distribution of patients by diagnosis is shown in table 1. An assessment of the frequency of detection of respiratory diseases in samples of subjects showed that most often they were diagnosed with bronchial asthma.

Analysis of complaints indicating pathology of the respiratory system in children living in Osh showed that from the group of healthy children, only one child (2.6%) had shortness of breath, while in group 2A this symptom was observed significantly more often ($p< 0.05$) – in 13 children (38.2%) (Table 2). Difficulty breathing, suffocation was noted in 5 subjects (14.7%) of group 2A,

TABLE 1:

Frequency of detection of respiratory diseases in children living at different altitudes above sea level

Diseases	Control (n=34)		Central lock (n=40)		Tr (n=30)	
	Abs.	%	Abs.	%	Abs.	%
Allergic rhinitis	11	32.4	10	25.0	8	26.7
Chronical bronchitis	8	23.5	ele.	27.5	9	30.0
Bronchial asthma	12	35.3	15	37.5	ele.	36.7
Chronic sinusitis	3	8.8	4	10.0	2	6.6

Table 2:

Frequency of complaints indicating pathology of the respiratory system in children living at different altitudes above sea level, (Abs. (%))

Complaints	Children living in Osh (880 m above sea level)		Children living in With. Gulcho (1400 m above sea level)		Children living in the village. Daroot-Korgon (3000 m above sea level)	
	Group 1A (n=38)	Group 2A (n=34)	Group 1B (n=35)	Group 2B (n=40)	Group 1C (n=32)	Group 2C (n=30)
Dyspnea	1 (2.6)	13 (38.2)*	3 (8.6)	18 (45.0)*	2 (6.3)	17 (56.7)*
Difficulty breathing, suffocation	-	5 (14.7)	-	15 (37.5)	-	16 (53.3)
Cough	-	14 (41.2)	2 (5.7)	22 (55.0)*	4 (12.5)	24 (80.0)*
Nasal congestion	5 (13.2	25 (73.3)*	9 (25.7)	32 (80.0)*	12 (37.5)	28 (93.3)*
Feelings of heaviness in the paranasal sinuses	-	11 (32.4)	-	15 (37.5)	-	19 (63.3)

Notes: * - differences are significant ($p<0.05$) relative to the corresponding values of groups 1 (A, B, C) according to the $\chi 2$ criterion

cough - in 14 children (41.2%) from this group, sensations of heaviness in the paranasal sinuses - in 11 children (32.4%) with respiratory diseases. None of the healthy children had such complaints. 5 children (13.2%) from group 1A complained of nasal congestion, while in group 2A the value of this indicator was statistically significantly higher – 73.3% (25 cases, $p<0.001$).

An assessment of children's complaints indicating pathology of the respiratory system in children living at an altitude of 1400 *m* above sea level showed that in the main group there were complaints of shortness of breath, cough, and nasal congestion significantly more often than in the comparison group. More than a third of children in group 2B complained of difficulty breathing and suffocation; children from this group also had a feeling of heaviness in the paranasal sinuses, while children from group 1B had no such complaints.

Similar were the ratios of the frequency of complaints indicating pathology of the respiratory system in children living in the village Daroot-Korgon (3000 *m* above sea level). A comparison of the characteristics of complaints in children living at different altitudes above sea level showed the following. The frequency of manifestations of shortness of breath in children with respiratory diseases increased significantly with increasing level of the area of residence above sea level; this complaint was noted in more than half of the children living in the village. Daroot-Korgon (3000 *m* above sea level) - in children of group 2B, statistically significantly more often ($p<0.05$) than in group 2A.

The frequency of complaints of difficulty breathing and suffocation in children living at different altitudes above sea level and in children with respiratory diseases increased with increasing level of the area of residence above sea level. This complaint was noted in 53.3% of children living at an altitude of 3000 *m* above sea level and in 37.5% of patients with respiratory diseases living at an altitude of 1400 *m*. Moreover, in both groups the values of these indicators were statistically significantly higher ($p<0.05$) corresponding value in group 1B – in children living in Osh.

Cough was observed in 80% of children with respiratory diseases living at the maximum altitude above sea level. The value of this indicator was significantly higher ($p<0.05$) than those in groups of children 2A and 2B, where its level was 41.2% and 55.0%, respectively.

Complaints about nasal congestion were noted in the vast majority of children with respiratory diseases living at different altitudes above sea level, most often at an altitude of 3000 *m*. As noted above, only children with respiratory diseases complained of shortness of breath, and the frequency of this was maximum complaints from children living in the village Daroot-Korgon (3000 *m* above sea level).

Analysis of the characteristics of the surface activity of endonasal washes and condensate of exhaled air in children living in Osh showed that children with signs of respiratory diseases had statistically significantly higher ($p<0.05$) than healthy children, the values of minimum surface activity

TABLE 3.

Indicators of surface activity of endonasal washouts and condensate of exhaled air in children living at different altitudes above sea level (M±m)

Indicators	Children living in Osh (880 m above sea level)		Children living in the villageGulcho (1400 m above sea level)		Children living in village Daroot-Korgon (3000 m above sea level)	
	Group 1A (n=38)	Group 2A (n=34)	Group 1B (n=35)	Group 2B (n=40)	Group 1C (n=32)	Group 2C (n=30)
Minimum surface tension of nasal washes, (mN/m)	33.5±1.3	38.2±2.4*	32.1±1.3	40.5±2.4*	30.8±3.1	44.8±4.8*
Maximum surface tension of nasal washes, (mN/m)	51.4±0.9	55.2±2.6	48.6±1.9	57.8±2.6*	45.7±4.5	61.3±3.7*
IS index of nasal lavages	0.57±0.08	0.47±0.06*	0.55±0.08	0.45±0.06	0.52±0.07	0.42±0.08
Minimum surface tension EAC, (mN/m)	44.5±0.12	47.4±0.09	42.8±0.12	49.0±0.09	44.7±3.6	52.7±2.4*
Maximum surface tension EAC, (mN/m)	61.3±1.5	68.2±3.2*	62.9±1.5	72.8±3.2*	64.5±4.0	74.5±6.5*
IS Index EAC	0.43±0.05	0.32±0.05*	0.41±0.05	0.35±0.05*	0.39±0.04	0.31±0.02*

NOTES: * - differences are significant ($p<0.05$) relative to the corresponding values of groups 1 (A, B, C) according to the Mann-Whitney test

tension (TN) of nasal lavages and maximum surface tension of the EAC (Table 3).

The values of other indicators of TN of nasal lavages and EAC also tended to increase relative to the corresponding values in the control group, but no significant differences were established. At the same time, in children of the main group, the stability index (IS) and EAC indices were significantly reduced ($p<0.05$) compared with the corresponding parameters in the control group.

Comparison of surface activity indicators of endonasal washes and EAC in children living in the village Gulcho (1400 *m* above sea level) showed similar ratios of the values of these parameters. At the same time, the children of the main group had a significantly reduced ($p<0.05$) index of the IS EAC. Analysis of the characteristics of the surface activity of endonasal washes and condensate of exhaled air in children from the village Daroot-Korgon (3000 *m* above sea level), showed that in children with respiratory diseases, the values of the minimum and maximum TN of nasal washes, minimum and maximum TN EAC. In the children of the main group, a statistically significant decrease ($p<0.05$) in the IS of EAC was noted.

A comparison of the levels of minimal TN of nasal lavages in children living at different altitudes above sea level showed that in the control groups they practically did not differ. In the main groups, the maximum value of this parameter was in children living in the village Daroot-Korgon at an altitude of 3000 *m* above sea level. The value of the indicator was significantly higher ($p<0.05$) than that in group 2A ($p<0.05$). The ratio of the maximum surface tension values of nasal lavages in children living at different altitudes above sea level was similar.

A comparison of IS values in children living at different altitudes above sea level showed that in control groups the values of this indicator did not differ significantly. In the main groups, the minimum value of this parameter was in children living in the village Daroot-Korgon at an altitude of 3000 *m* above sea level. The value of the indicator was significantly lower than that in group 2A ($p<0.05$).

An evaluation of the levels of minimum TN EAC in children living at different altitudes above sea level showed that in the control groups they practically did not differ. In the main groups, the maximum value of this parameter was in children living in the village Daroot-Korgon at an altitude of 3000 *m* above sea level. The value of the indicator was significantly higher than that in group 2A ($p<0.05$). An assessment of the levels of maximum TN EAC showed that if in the control groups the values of these indicators practically did not differ, then in the main groups the level of this parameter was maximum in children living in the village Daroot-Korgon at an altitude of 3000 *m* above sea level, although no statistically significant inter-

group differences were found. Comparison of the levels of IS EAC showed the absence of significant intergroup differences in this indicator.

A study of the activity of free radical oxidation processes and the state of the antioxidant system of exhaled air condensate in children living in Osh (880 *m* above sea level) showed that children with signs of respiratory diseases had significantly more ($p<0.05$) than in the control group, the levels of hydroperoxides, diene conjugates in EAC, and the oxidative index were also significantly increased (Table 4). At the same time, in group 2A the concentration of total lipids in the EAC was significantly lower ($p<0.05$) than in group 1A.

Analysis of these indicators in children living in the village Gulcho (1400 *m* above sea level), testified that in children with signs of respiratory diseases, the concentrations of hydroperoxides, diene conjugates in EAC were statistically significantly higher ($p<0.05$) than in the control group, and were also significantly higher ($p<0.05$) oxidative index. At the same time, in group 2A the concentration of total lipids in the EAC was statistically significantly lower ($p<0.05$) than in group 1B. Studying the activity of free radical oxidation processes and the state of the antioxidant system of EAC in children living in the village Daroot-Korgon (3000 *m* above sea level) showed similar ratios of these indicators.

An assessment of the level of total lipid content in the examined children showed that in the control groups the values of this parameter decreased with decreasing altitude above sea level. In the main groups, the values of this indicator were maximum in children living in Osh, while in patients from groups 2B and 2C its values were significantly lower than in group 2A ($p<0.05$).

Comparison of the levels of EAC hydroperoxides in the examined children showed an increase in its values with increasing altitude of residence, both in the control and in the main groups. An assessment of the concentrations of diene conjugates showed that in the main groups the maximum value of this parameter was in children living in the village Daroot-Korgon at an altitude of 3000 *m* above sea level. The value of the indicator was significantly higher than that in group 2A ($p<0.05$).

A comparison of the values of the oxidative index in children living at different altitudes above sea level indicated the absence of pronounced differences in this indicator in the control groups. At the same time, in the main groups the maximum value of this indicator was in children living in the village Daroot-Korgon at an altitude of 3000 *m* above sea level. The value of the indicator was significantly lower than those in groups 2A and 2B ($p<0.05$).

Discussion

Over the past three decades, the world has seen an increase in the incidence of respiratory system diseases in the child population, including those diseases whose pathogenesis is based on impaired immunity and the development of allergic reactions, such as bronchial asthma, allergic bronchitis and rhinitis [*Siroux V, Bouzigon E, 2019; Lukacs N, Huang Y, 2020*]. Although the etiology of allergic diseases is largely determined by both genetic and environmental factors, including sensitization to aeroallergens, which is associated mainly with environmental factors (climatic conditions, alti-

Table 4.

Indicators of free radical oxidation and activity of the antioxidant system of exhaled air condensate in children living at different altitudes above sea level (M±m)

Indicators	Children living in Osh (880 m above sea level)		Children living in the villageGulcho (1400 m above sea level)		Children living in villageDaroot-Korgon (3000 m above sea level)	
	Group 1A (n=38)	Group 2A (n=34)	Group 1B (n=35)	Group 2B (n=40)	Group 1B (n=32)	Group 2B (n=30)
Total lipids, (mg/l)	0.112±0.011	0.092±0.006*	0.106±0.009	0.082±0.005*	0.098±0.008	0.083±0.005*
Hydroperoxides, (mg/l)	0.046±0.009	0.073±0.012*	0.054±0.004	0.087±0.011*	0.062±0.011	0.089±0.008*
Dieneconjugates, (mg/l)	0.014±0.003	0.034±0.007*	0.025±0.002	0.049±0.009*	0.021±0.005	0.057±0.005*
Oxidative index	0.438±0.051	0.588±0.063*	0.457±0.041	0.625±0.055*	0.473±0.037	0.692±0.046*

Notes: * - differences are significant ($p<0.05$) relative to the corresponding values of groups 1 (A, B, C) according to the Mann-Whitney test

tude above sea level, air pollution, temperature, humidity, etc.) [*Sheffield P et al., 2011*].

The role of free radical oxidation processes in a number of homeostasis processes has now been described; it is obvious that these changes are manifestations of changes occurring at the molecular and cellular level in the mucous membrane of the upper respiratory tract during the pathologies under consideration. In particular, hyperproduction of reactive oxygen species is the most important characteristic of bronchial asthma. These processes contribute to an increase in the severity of inflammation, vasoconstriction and remodeling [*Di Meo S et al., 2016; Zhang J et al., 2016*].

Our studies showed that the examined children with respiratory diseases complained of shortness of breath, difficulty breathing, suffocation, cough, nasal congestion, as well as a feeling of heaviness in the paranasal sinuses, much more often than in the control groups. At the same time, an increase in their frequency was revealed with increasing altitude of the children's areas of residence above sea level: the frequency of complaints was maximum among those surveyed from the village Daroot-Korgon (3000 *m* above sea level).

Also, in children with respiratory diseases, an increase in the activity of free radical oxidation processes was observed, in particular, a decrease in the levels of total lipids along with an increase in the concentrations of hydroperoxides, diene conjugates and the oxidative index in the exhaled air condensate. These changes were most pronounced in children with respiratory pathologies living at maximum altitude above sea level.

Indicators of the surface activity of endonasal swabs and EAC were also increased in sick children compared to the group of healthy subjects, while the values of the parameters of the maximum and minimum surface tension of these biosubstrates increased significantly with increasing altitude of children with respiratory diseases above sea level.

It should be noted that the individual reports in the literature on the results of examinations of people with respiratory diseases living at different altitudes above sea level are very contradictory. Thus, the purpose of the study by Ozkaya E. et al. (2015) was a study of the nature of sensitization in asthmatic children living in different high-altitude areas: two largest Turkish cities, Istanbul (at sea level) and Erzurum (highlands). The study included 512 children with bronchial asthma (6-15 years) from Istanbul and 609 from Erzurum (eastern Turkey, at an altitude of 1800 *m*). All participants underwent skin testing for common inhalant allergens, spirometry, total IgE levels, and clinical examination. It was found that the rate of positive sensitization to aeroallergens in children with asthma living at sea level was statistically higher than in children living in the high-altitude group ($p = 0.001$, odds ratio (OR) was 4.9, confidence interval (CI) 3.67–6.459). At the same time, sensitization to pollen in asthmatic children living at high altitudes was significantly higher than in children living at sea level ($p=0.00$, OR=2.6, CI 1.79–3.87). According to the authors, children with asthma living at high altitudes have higher levels of sensitivity to pollen allergens but lower levels of sensitization to mites than children living at sea level in Turkey. Different climate conditions and altitude may influence sensitization to aeroallergens in children with asthma [*Ozkaya E et al., 2015*].

The results obtained by these authors suggested that high altitude is a major determinant of pollen sensitization in children with asthma, in addition to climatic conditions (e.g., temperature, humidity and air pollution) [*Ozkaya E et al., 2015*].

In general, the data obtained by us and other authors confirmed that the identified biochemical changes confirm the need for a thorough study of the medical history, risk factors and living conditions when examining children with respiratory diseases when choosing treatment tactics for these patients [*Havet A et al., 2019; Traina G et al., 2022; Cordiano R et al., 2023; Dondi A et al., 2023*]. Based on taking into account these data, optimization of the balance of the body's pro- and antioxidant systems should become the most important mechanism and a necessary condition for a complex of therapeutic and preventive measures carried out for children with diseases of the respiratory system.

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