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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2023;12(2):466-9

Regional peculiarities of specific immunity in inhabitants of different mountain heights of the Kyrgyz Republic

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Received 20 February 2023; Accepted 05 May 2023
Available online 26.05.2023 with doi: 10.5455/medscience.2023.02.027

Abstract

Kyrgyzstan's challenging natural conditions and fragile mountain ecosystems can weaken the immune system of individuals residing permanently in high-altitude areas. Our study aimed to explore specific immune protection indicators in healthy populations from the Chui and Naryn regions at varying mountain altitudes. We assessed percentages of CD3+ (T-lymphocytes), CD20+ (B-lymphocytes), CD4+ (T-helper lymphocytes), CD8+ (cytotoxic T-lymphocytes), IRI (immunoregulatory index), CIC (circulating immune complexes), and quantified immunoglobulins of classes A, M, and G. Using immunofluorescent methods and monoclonal antibodies; we determined the percentages of CD3+, CD20+, CD4+, and CD8+. Radial immunodiffusion was used to quantify immunoglobulins of classes A, M, and G, while Falk's method helped study CIC levels in blood sera. The participant count was based on statistical expert recommendations and G power analysis. The analysis revealed a decrease in the total number of T-lymphocytes (CD3+), primarily due to reduced T-helper and cytotoxic T-lymphocyte subpopulations. However, a significant increase in cytotoxic T-lymphocytes (CD8+) was observed among high-altitude residents. Mountain residents exhibited wide-ranging individual fluctuations for each immunoglobulin class. Our findings suggest varying degrees of immune mechanism disruptions, which maintain natural protection and internal environment constancy at different altitudes, resulting in a mixed type of cellular and humoral immunity suppression. These results emphasize the need for further research in the region and consideration of altitude when implementing disease prevention strategies related to the immune system for the local population.

Keywords: Immune system, specific protection factors, T-lymphocytes, B-lymphocytes, immunoglobulins, low mountains, high mountains

Introduction

It is widely acknowledged that high-altitude factors can impact various bodily functions. Conducting immunological studies and investigating immune system features in the population is relevant to understanding the effects of climatic, geographical, and environmental factors on public health [1-4].

Kyrgyzstan's unique natural conditions and the vulnerability of mountain ecosystems are challenging. The predominance of highly differentiated relief creates special living conditions in the mountains, valleys, and plains, where the main settlements are concentrated. According to bioclimatic zoning, about 4 million people (79%) live in the territory (17%) classified as a zone of comfort for life, while around 1 million people (19%) live in the relative or compensated comfort territory at heights ranging from 1500 to 2200 m. The remaining 2% of the population live at altitudes above 2200 m in uncompensated bioclimatic comfort conditions [5,6]. Permanent residence at high altitudes is thought to lead to a decrease in the body's immune defense capacity [3,7]. Therefore, it is of significant theoretical and practical interest to

CITATION
Tiumonbaeva N, Kazybekova A, Kasymalieva K, Soburov K. Regional peculiarities of specific immunity in inhabitants of different mountain heights of the Kyrgyz Republic. Med Science. 2023;12(2):466-9.

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DOI: 10.5455/medscience.2023.02.027

study specific immunity indicators in the inhabitants of different mountainous regions of the republic.

It is well-established that the mechanisms of the specific immune response to an antigen involve the humoral immune response, mediated by antibodies in blood plasma, and the cellular immune response, mediated by immune system cells without antibodies. The cellular part of the immune system, primarily the T cellular part, also plays a crucial role in resistance development [8].

In addressing this issue, we assessed the immune reactivity of the inhabitants of the mountainous regions of Chui and Naryn, which vary in altitude, natural and climatic conditions, and the level and nature of industrial and agricultural development. This area involves studying "immune polymorphism" among the population of these regions as a whole and separately for each region.

This study aimed to comparatively assess immune reactivity in people residing in different mountainous regions of the Chui and Naryn regions.

Material and Methods

The study examined the main indices of immunity in a practically healthy population. The parameters of specific resistance were determined for 244 local inhabitants living in the mountainous regions of Chui and Naryn oblasts, including Suusamyr (2200 m), At-Bashy (2600 m), and Ak-Kyia (2800 m). The control group consisted of 65 people of the same age who lived in a relatively comfortable region called Tash-Dobo (930 m). The study included people who had lived in the region for at least 5 years.

The research was conducted at the Laboratory of the Physiology of the Immune System at the Institute of Mountain Physiology and Medicine of the National Academy of Sciences of the Kyrgyz Republic. The percentage of total T-lymphocytes, including CD4+ (T-helper cells), CD8+ (cytotoxic cells), CD20+ (B-lymphocytes), monoclonal antibodies were determined using indirect immunofluorescence and monoclonal antibodies to clusters of differentiation [2]. The percentage of lymphocytes and subpopulations, including CD3+ (total T-lymphocytes), CD4+ (T-helper cells), CD8+ (cytotoxic cells), and CD20+ (B-lymphocytes), was determined using monoclonal antibodies labeled with immunofluorescent pigments [2]. The radial immunodiffusion method was used to quantify the immunoglobulins of classes A, M, and G [2]. To identify any polarization in the composition of subpopulations, the immunoregulatory index (IRI), which is the ratio of the percentage content of subpopulations of phenotypes CD4+ and CD8+, was determined.

Diffusion and immunoprecipitation result in a precipitation ring in the agar, and the diameter of this ring depends on the concentration of the antigen in the serum. The diameter of the precipitation ring is directly proportional to the logarithm of the sample concentration. By measuring the diameter of the ring in the test samples, the concentration of immunoglobulins of the class being tested was determined in mg protein per 100 ml of serum (mg %), using a calibration curve, and then converted to mg/L. The level of circulating immune complexes (CIC) in the blood serum was investigated using the Falk method [9]. The principle of this method is based on the nephelometry of immunoglobulin monomers in immune complexes of different solubility in the presence of polyethylene glycol (PEG-6000) in the medium. Determining serum CIC levels is one of the diagnostic techniques used to determine the severity and activity of an immunopathological process.

Statistical Analysis

The number of participants used in the study was determined based on the recommendations of statistics experts and G power analysis. The statistical processing was performed using standard programs such as Microsoft SPSS/Minitab. The material was subjected to variational-statistical processing, which included determining the arithmetic mean series, standard deviations, confidence intervals, and Student's t-test. The confidence level used in the study was 95%, as is customary in biological and medical research. For clarity, the confidence limits for each average value were calculated, followed by the construction of bar graphs. The materials were processed using the Excel program on a computer.

Results

We compared the cellular and humoral immunity indices of inhabitants living at various altitudes in the designated regions to achieve our goal. We found significant differences between the indices by conducting a comparative analysis of the immune indices of residents in both the control and studied regions (Table 1).

In our study, the analysis of changes in the primary populations of lymphocytes revealed a decrease in the overall number of T-lymphocytes (CD3+), including subpopulations of both T-helper and cytotoxic T-lymphocytes. Among the residents of the Chui region, there was a more significant decline in the latter (Table 1). Nonetheless, we observed a significant increase in the number of cytotoxic T-lymphocytes (CD8+) among the residents of high-altitude regions, specifically in c. At-Bashy and c.Ak-Kyia of Naryn oblast.

Our observations showed a wide range of individual fluctuations in the synthesis of each immunoglobulin class among the residents of mountainous regions. Among permanent residents of high-altitude areas (2500–2800 m), there was a significant reduction in the synthesis of IgM and IgA ($P<0.05$), except for residents of c.Suusamyr (IgG) and c.Ak-Kyia (IgM). Meanwhile, the synthesis of immunoglobulin G in the blood serum of highland residents (c.Suusamyr) was slightly higher than that of residents in c.Tash-Dobo (930 m). However, this index was significantly lower in inhabitants of highland areas such as c.At-Bashy (Figure 1).

When the results were evaluated according to gender, it was determined that there was no statistical difference.

DOI: 10.5455/medscience.2023.02.027

Table 1. Comparative indicators of cellular immunity in residents of different mountain heights in Chui and Naryn oblasts

Indicators	Chui Oblast				P	Naryn Oblast				P
	village. Tash-Dobo, Alamudun district, 930 m, n=65		village. Suusamyr, Jaiyl district, 2200 m, n=63			village. At-Bashy, At-Bashy region, 2300-2500 m, n=65		village. Ak-Kyia, Kochkor district, 2800 m, n=51		
	Male n=44	Female n=21	Male n=51	Female n=12		Male n=47	Female n=18	Male n=39	Female n=12	
CD3+ %	47.6±0.14	44.7±0.32	43.88±0.39	44.77±0.23	>0.01	34.7±0.24	38.1±0.43	30.2±0.13	32.4±0.21	<0.01
CD20+ %	18.24±0.43	20.02±0.16	18.37±0.21	19.92±0.78	>0.01	24.17±0.51	24.82±0.82	24.2±0.71	21.86±0.56	<0.01
CD4+ %	26.09±0.74	26.77±0.13	16.48±0.78	14.33±0.19	<0.001	21.02±0.80	19.9±0.35	13.0±0.75	15.0±0.04	<0.005
CD8+ %	13.10±0.18	15.45±0.18	13.06±0.1	13.02±0.1	<0.001	18.09±0.17	19.73±0.92	17.9±0.04	16.94±0.39	<0.01
IRI %	1.62	1.93	1.09	1.31	<0.01	1.12	1.07	0.8	0.8	>0.01
CIC %	86.7±0.05	88.1±1.7	109.4±2.4	111.4±4.3	<0.05	95.8±4.2	95.06±1.0	112.0±0.3	115.0±4.4	>0.01

* - the result is statistically significantly different from the data obtained in the low mountains c. Tash-Dobo (P<0.05). CD3+ - T-lymphocytes, CD20+ - B-lymphocytes, CD4+ - helper T-lymphocytes, %; CD8+ - cytotoxic T-lymphocytes, %; IRI - immunoregulatory index; CIC - circulating immune complexes

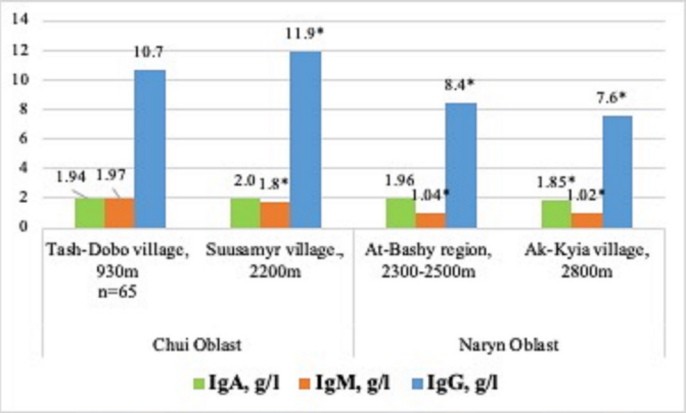

Figure 1. Indicators of major classes of immunoglobulins in residents of different altitudes of Chui and Naryn oblasts - the result is statistically significantly different from the data obtained in the lowlands of Tash-Dobo (P<0.05)

Discussion

Our observations showed a wide range of individual fluctuations in the synthesis of each immunoglobulin class among the residents of mountainous regions. Among permanent residents of high-altitude areas (2500–2800 m), there was a significant reduction in the synthesis of IgM and IgA (P<0.05), except for residents of c.Suusamyr (IgG) and c.Ak-Kyia (IgM). Meanwhile, the synthesis of immunoglobulin G in the blood serum of highland residents (c.Suusamyr) was slightly higher than that of residents in c.Tash-Dobo (930 m). However, this index was significantly lower in inhabitants of highland areas such as c.At-Bashy (Figure 1).

Normally, cytotoxic cells and antibodies should produce enough to eliminate a specific antigen [10]. However, the insufficient activity of T-suppressors in residents of Chui Oblast results in the dominance of T-helper influence, contributing to a stronger immune response characterized by pronounced antibody production and/or prolonged activation of T effectors. Conversely, excessive T-suppressor activity in Naryn residents leads to rapid suppression and interruption of the immune response, and even phenomena of immunological tolerance where the immunological response to antigen hardly develops. This can result in the development of autoimmune and allergic processes with a strong immune response [11]. The high functional activity of T-suppressors does not allow for an adequate immune response to develop. These data suggest excessive stimulation of the T-cell link of the immune system under the influence of factors of different mountain heights [7, 12].

The ratio of peripheral circulating T-helper-CD4+ cells to T cytotoxic-CD8+ cells is a key indicator of the balance between T-lymphocytes. If this ratio is below or above certain values, it can provide important clues about the immune system [13]. For the villagers of Chui Oblast, the ratio was close to the normergic state at 1.81–1.19 (over 2.5, indicating the activity of Tx). In contrast, the immunoregulatory index was much lower in the villages of Naryn Oblast, ranging from 1.1–0.8, which characterizes the insufficient activity of T-helper cells (an index of less than 1.0 indicates immunodeficiency).

An increased level of CIC in the blood can result from inadequate absorption function of micro- and macrophages. CIC formation is a natural defense mechanism of the body, leading to the rapid removal of endogenous and exogenous antigens. Typically, phagocytes capture these antigens, destroy them, and remove them from the body [14]. Increased levels of circulating immune complexes in mountainous areas may damage the receptor apparatus of T-lymphocytes. This process can lead to systemic or organ pathology.

The relatively low percentage of T-lymphocytes among high-altitude inhabitants is noteworthy when compared to the corresponding values in the healthy population of Chui Oblast (44.55% vs. 31.70%). The average regional value of this indicator for residents of Naryn Oblast (34.3%) was significantly lower than that of residents in Chui Oblast (45.7%).

An increase in the relative number of B-lymphocytes is known to occur in autoimmune and allergic diseases and is also associated with the presence or absence of plasma cells in the clinical blood count, as well as the levels of immunoglobulins A, M, and G [15,16]. Thacke et al. [17] reported decreased leukocyte and neutrophil counts during a 4-h hypoxia equivalent to 4000 m altitude. Ghobadi et al. [18] reported a significant increase in

DOI: 10.5455/medscience.2023.02.027

lymphocyte and neutrophil levels caused by hypoxia at high altitudes. Residents of Naryn Highlands also showed a significant increase in the blood content of B-lymphocytes carrying the CD20+ antigen, which was associated with the intensification of immunoglobulins A and G synthesis. In this case, it's possible to talk about restructuring the immune system functioning in high-altitude inhabitants. Further studies in a larger population are needed to evaluate these findings according to parameters such as gender, race, and age.

Conclusion

In conclusion, we have observed that the indicators of specific immunity in the almost healthy population of the highland area of Naryn Oblast are reduced compared to the standards for residents of Chui Oblast (Tash-Dobo) and refer to a mixed type with suppression of cellular and humoral immunity. This reduction is likely associated with the region's climatic, geographical, and environmental features. The changes in immune reactivity we have identified indicate different levels of immune mechanism violations in maintaining natural protection and constancy of the body's internal environment at different altitudes of mountainous terrain. Therefore, monitoring various immune parameters at regular intervals is recommended to prevent health problems in people living in high-altitude areas. Further research is needed to understand the mechanism of the effects of altitude differences on the immune system.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The study was supported by National Academy of Sciences of the Kyrgyz Republic.

Ethical approval
The study was approved by Bioethics Committee Ministry of Health of the Kyrgyz Republic No. 04-1/4-5896.

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