Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 485 - 493
Received 16 February 2021; Accepted 08 March 2021.

Estimation of Essential Microelements and their Diagnostic Significance in Patients with Occupational Allergies

Galina M. Bodienkova[1*], Svetlana S. Timofeeva[2], Oksana V. Ushakova[3], Lyudmila G. Lisetskaya[4]

[1*]East-Siberian Institute of Medical and Ecological Research, Russian Federation.
*Corresponding author. E-mail: immun11@yandex.ru
[2]Irkutsk National Research Technical University, Russian Federation.
[3]East-Siberian Institute of Medical and Ecological Research, Russian Federation.
[4] East-Siberian Institute of Medical and Ecological Research, Russian Federation.

ABSTRACT

Allergopathology is accompanied, among other things, by a metabolic disorder of a number of microelements that are involved in the regulation of the immune response and in the enzymes metabolism of lymphocytes antioxidant protection. The present research aimed to assess the content and diagnostic significance of essential microelements (zinc, copper, iron) in urine, blood serum and lymphocytes in patients with occupational allergies depending on the form of manifestation and the severity.

Methods. 68 patients with occupational allergies of the skin and respiratory organs were examined. The content of zinc, copper and iron was determined by atomic absorption analysis in urine, blood serum and lymphocytes.

Results. It was established that the development and course of occupational allergic diseases is accompanied by an imbalance of microelements, characterized by decreased concentration of zinc and copper in the urine, increased concentration of copper in lymphocytes and of iron in the blood serum. The content of zinc in urine and in lymphocytes decreases with increasing severity of the allergic process, while the content of copper increases, which indicates the antagonism of these microelements. In patients with skin and respiratory organs pathologies, changes in most microelements in biomaterials are unidirectional and repeat the quantitative patterns of their content established in general for all the subjects. However, in patients with skin diseases, the level of zinc in lymphocytes is more than 2 times higher than in patients with respiratory pathology.

Conclusion. The established imbalance of the main microelements in patients with occupational allergic diseases requires targeted correction. The research substantiated the most sensitive and specific indicators in the diagnosis of occupational skin allergies (content of zinc and copper in urine) and of respiratory organs (zinc and copper in urine, iron in blood serum).

KEYWORDS

Occupational Allergies, Essential Microelements, Imbalance, Diagnostic Significance.

Introduction

The priority of the social policy and healthcare of the state is to preserve the health of the working population, which contributes to strengthening the country's labor potential and the economic well-being of society [1, 2, 3]. Allergies are at the top in the structure of chronic

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 485 - 493
Received 16 February 2021; Accepted 08 March 2021.

occupational pathology; however, morbidity rates vary significantly across industries [4, 5, 6]. As known, the development and course of occupational diseases can be influenced by the characteristics of modern production – the nature of the influencing factors and their complex and combined impact [7].

The relevance of the study of occupational allergic pathology in the Baikal region is due to the high concentration of industries, most of which are characterized by insufficiently high technologies and outdated equipment; a significant number of jobs do not meet sanitary standards [8, 9, 10]. Both worldwide and in Russia, awareness of the connection between the disease and the profession is vital for maintaining the health of the working population. To identify stable causal relationships of health disorders with the working environment factors, it is necessary to substantiate and use biomarkers and biological response to exposure to sensitizing substances. In this regard, preventive and personalized medicine pays much attention to the molecular and cellular mechanisms of occupational allergies in order to substantiate new informative markers of early and differential diagnosis. Despite numerous studies of the formation mechanisms, clinical features, diagnostics and prevention of the adverse effects of industrial allergens on the body [11, 12, 13, 14, 15, 16, 17], some theoretical and practical issues still remain unresolved. Recent studies established that the formation of allergic pathology is accompanied by a metabolic disorder of a number of microelements in the body [18, 19, 20]. Such essential trace elements as copper, zinc and iron are involved in the regulation of the immune response; they control the secretory activity of mast cells and the local protection of the mucous membranes [21, 22, 23]. However, scientific literature does not cover enough the content of microelements in biomaterials in patients with occupational allergies. According to modern concepts, the intracellular pool of microelements is the most stable and plays an important role in the metabolic processes of enzymes of antioxidant protection of cells [24, 25].

In this regard, a deeper study of the role of the main microelements in the development and course of occupational allergies is important for improving the diagnostic methodology.

The present study aimed to assess the content and diagnostic significance of essential microelements (zinc, copper, iron) in urine, blood serum and lymphocytes in patients with occupational allergies depending on manifestation and severity.

Methods

On the basis of the East-Siberian Institute of Medical and Ecological Research clinic, 68 patients with an established diagnosis of occupational allergic pathology were examined (all female, aged 45.4 ± 1.0, work experience in contact with allergens was 17.4 ± 0.9 years). The diagnosis was established taking into account the allergic history, clinical manifestations, data of objective and allergological examination, information about the contact with allergens at work from the sanitary and hygienic characteristics of the worker. Depending on the clinical form of the disease, patients were divided into the following subgroups: 38 patients (55.9%) with skin pathology, 30 patients (44.1%) with respiratory pathology. In the group with skin pathology, contact-allergic dermatitis was diagnosed in 15 patients, occupational urticaria in 4, occupational eczema in 19 patients. The main clinical forms in the group with respiratory pathology are bronchial asthma in 29 examined patients (mild in 5, moderate in 19, severe in 5 people). The control group consisted of 44 people (all female, aged 37.5 ± 1.2). The history of the examined

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 485 - 493
Received 16 February 2021; Accepted 08 March 2021.

patients did not reveal any allergic pathology or allergic reactions; an objective examination did not reveal any skin or respiratory organs pathology either. Microelements in the biosubstrates of the examined patients were determined by instrumental atomic absorption analysis on a Spectrum-5-1 spectrophotometer. Zinc concentration was determined in fresh daily urine without preliminary preparation. To determine copper and iron, urine samples were preserved with nitric acid, then mineralized by decomposing the sample with concentrated nitric acid [26]. Fasting blood serum from the cubital vein was mineralized in autoclaves. To measure the concentration of copper, the absorption of radiation with a wavelength of 324.8 nm was used, 213.9 nm for zinc, and 248.3 nm for iron.

The results were statistically processed using the STATISTICA 6.0 software package (StatSoft, USA). To compare the related groups, the arithmetic mean (M) and the arithmetic mean error (m) were calculated. The statistical significance of the differences was assessed using the Student's test (with a normal distribution). The level of significance was taken as $p < 0.05 – 0.001$. Using a four-field table, the sensitivity and specificity of the diagnostic test results were calculated [27].

Patients' examination was carried out in accordance with the ethical standard of the Helsinki Declaration of the World Association 'Ethical Principles for Scientific Medical Research with Human Participation', as amended in 2000 and 'Rules of Clinical Practice in the Russian Federation' approved by Order of the Ministry of Health of the Russian Federation No. 266 of June 19, 2003, with the informed consent of patients and on the conclusion of the ethical committee of the Scientific Center for Medical Ecology of the East Siberian Scientific Center of the Russian Academy of Medical Sciences, which included the East-Siberian Institute of Medical and Ecological Research (Protocol No. 5 of October 14, 2012).

Results

Concentrations of microelements in urine, blood serum and lymphocytes in patients with occupational allergies are presented in Table 1.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 485 - 493
Received 16 February 2021; Accepted 08 March 2021.

Table 1. Content of microelements in biomaterials and in lymphocytes in patients with occupational allergies

Microelements	**Biomaterials**	**Unit**	**Patients with professional allergies (*n* = 68)**	**Comparison group (*n* = 44)**
Zinc	Urine	mg/dm^3	0.20±0.02*	0.29±0.03
Copper	Urine	mg/dm^3	1.01±0.2*	2.99±0.2
Zinc	Serum	mg/dm^3	0.73±0.03	0.67±0.05
Copper	Serum	mg/dm^3	0.82±0.03	0.74±0.03
Iron	Serum	mg/dm^3	4.36±0.55*	2.31±0.23
Zinc	Lymphocyte	nmol/mln	1.39±0.33	1.11±0.2
Copper	Lymphocyte	nmol/mln	0.20±0.04*	0.10±0.01*

Note: * - differences in indicators are statistically significant at $p < 0.05$.

Table 1 illustrates that the examined patients showed a statistically significant decrease in the concentration of zinc and copper in the urine compared with the comparison group. As for the blood serum, a significant increase in the concentration of iron in it ($p < 0.01$) and a tendency towards an increase in copper is noted. Analysis of the microelement status of immunocompetent cells - blood lymphocytes, the main participants in the allergic process – in the examined patients with allergic pathologies showed an increased content of copper in lymphocytes compared to the control indicators ($p < 0.001$). At the same time, the content of zinc in lymphocytes did not change significantly.

Particullarly interesting was the assessment of a significant ratio of Cu/Zn (which is one of the most important constants in the human body) in biosubstrates. The research revealed that in the blood serum of both the examined patients and those of the control group, the ratio of microelements is disturbed – the level of copper exceeds the level of zinc. However, in the lymphocytes of the examined individuals these ratios approach the norm – the level of zinc increases, while that of copper decreases and is equal to 1:10.

The analysis of the microelements level depending on the clinical form of the disease shows that the majority of indicators in patients with the skin and respiratory organs pathology in relation to the comparison group are unidirectional and repeat the quantitative patterns of the content of biometals established in general in all the subjects (Table 2).

Table 2. Comparative assessment of microelement content in patients depending on nosological form

Indicators	**Unit**	**Patients with skin pathology (*n* = 38)**	**Patients with respiratory organs pathology (*n* = 30)**	**Comparison group (*n* = 44)**
Zinc in urine	mg/dm^3	0.23±0.03	0.17±0.02°	0.29±0.03
Copper in urine	mg/dm^3	1.04±0.24°	0.97±0.39°	2.99±0.2
Zinc in serum	mg/dm^3	0.75±0.04	0.69±0.05	0.67±0.05
Copper in serum	mg/dm^3	0.81±0.03	0.85±0.07	0.74±0.03

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 485 - 493
Received 16 February 2021; Accepted 08 March 2021.

Iron in serum	mg/dm^3	4.90±0.6	3.60±0.6	2.31±0.23
Zinc in lymphocyte	nmol/mln	1.32±0.31*	0.51±0.12	1.11±0.2
Copper in lymphocyte	nmol/mln	0.22±0.07	0.15±0.04	0.10±0.02

Note: ° – differences in indicators are statistically significant between the control group and patients with pathology at $p < 0.001$; * – differences in indicators are statistically significant between patients with different forms of diseases at $p < 0.05$.

It is important to note that in patients with skin diseases, the level of zinc in lymphocytes is more than 2 times higher than in patients with respiratory pathology.

Analyzing the concentration of microelements in the biomaterials of the examined patients depending on the level of allergic processes (mild, moderate, severe), a pattern was established in the form of a feedback between the concentrations of zinc and copper in urine. Namely, the content of zinc in urine from mild to severe degree of the allergic process is statistically significantly reduced (0.3 ± 0.03 mg/L – mild degree, 0.18 ± 0.02 mg/L – moderate degree, 0.14 ± 0.04 mg/L – severe degree; $p < 0.05$). At the same time, the concentration of copper increases from mild to severe degree (0.61 ± 0.22 μg/L – mild degree, 1.12 ± 0.28 μg/L – moderate degree, 2.96 ± 0.32 μg/L – severe degree; $p < 0.05$). Against the background of a pronounced trend towards an increase in zinc concentration from moderate to severe degree, the copper level statistically significantly decreases from mild to severe (0.28 ± 0.03 nmol/mln and 0.15 ± 0.03 nmol/mln respectively; $p < 0,05$). The content of zinc and copper in blood serum did not change depending on the severity of the pathological process.

The established imbalance of the main essential microelements which increases with the severity of the pathological process, requires targeted correction in patients with occupational allergies.

To assess the reliability and validity of the diagnostic significance of the studied microelements, individual indicators of their sensitivity and specificity were calculated using a four-field table. The calculation results showed that the most sensitive for occupational allergies are: the content of zinc (78%), copper (79%) and iron (82%) in the blood serum. Highly sensitive and specific are such indicators as: urine zinc (sensitivity 73%, specificity 72%) and copper (sensitivity 76%, specificity 71%), and copper in lymphocytes (sensitivity 63%, specificity 61%).

The information content of indicators of microelements in biomaterials depending on the nosological form of the disease was of great interest. In occupational allergic dermatoses, sensitive and specific indicators are: urine zinc (sensitivity 76%, specificity 72%) and copper (sensitivity 73%, specificity 89%). In occupational allergic pathology of the respiratory system, the following sensitive and specific indicators were revealed: urine zinc (sensitivity 70%, specificity 93%) and copper (sensitivity 70%, specificity 85%), and serum iron (sensitivity 73%, specificity 72%).

Discussion

The study was based on literature data showing the important role of copper, zinc and iron in the

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 485 - 493
Received 16 February 2021; Accepted 08 March 2021.

regulation of immune responses [18, 19, 20, 21]. The established decrease in the concentration of zinc and copper in biosubstrates (urine, blood serum, lymphocytes) in patients with occupational allergies may indicate an increased body demand for these microelements and their intensive use in tissues, in particular, in the skin and mucous membranes. Of particular interest is the analysis of the microelement status of immunocompetent cells – blood lymphocytes, which are the main participants in the allergic process. The authors of the present research recorded an increase in copper in lymphocytes. It should be noted that the effects of copper on the immune system are dose-dependent, and therefore, excess copper may have an immunotoxic effect on the cells of the immune system. A number of sources [28, 29] state that the ability of microelements to influence various aspects of immune responses is the result of profound changes in lymphocyte metabolism. Attention is drawn to the altered ratio of Cu/Zn (a most important constant in the human body) in the serum and urine – 1:1 both in the examined patients and in the control group. According to the literature, the normal amount of zinc exceeds the amount of copper by at least 8 times [30].

Depending on the clinical form of the disease (pathology of the skin and of respiratory organs), the concentrations of most microelements are unidirectional. However, it is important to note that in patients with skin diseases, the level of zinc in lymphocytes is more than 2 times higher than in patients with respiratory pathology. The studies confirm the fact that T-lymphocytes are most sensitive to changes in the content of zinc in biomaterial, and B-lymphocytes are less sensitive. It is known that excessive zinc has an inhibitory effect on the immune system, while its physiological content stimulates the functional activity of the immune system. In previous studies, the authors showed that in patients with occupational skin allergies, an increased zinc content decreases the main subpopulations of T-lymphocytes, while the number of B-lymphocytes does not change. The revealed regularity in the form of a feedback between the concentrations of zinc and copper in urine (the content of zinc decreases from mild to severe allergic process, while copper increases) is consistent with literature data indicating the antagonism of these microelements [31]. Antagonistic relationships between the content of zinc and copper are also traced in lymphocytes. The established imbalance of the essential microelements, increasing with the severity of the pathological process, requires targeted correction in patients with occupational allergies. In this regard, informative sensitive indicators were established in the present research.

Conclusion

The development and course of occupational allergies is accompanied by an imbalance of microelements, characterized by decreased concentration of zinc and copper in the urine and by increased copper in lymphocytes and iron in the blood serum. The dependence of changes in microelements in biomaterials on the degree (mild, moderate, severe) of the pathological process in patients with occupational allergies was established. The content of zinc in urine and in lymphocytes decreases with increased severity of the allergic process, and that of copper increases, which indicates the antagonism of these microelements. The most sensitive and specific indicators in the diagnosis of occupational allergic skin pathology (content of zinc and copper in urine) and occupational allergic pathology of the respiratory system were substantiated (zinc and copper in urine, iron in blood serum).

Financing

The work was carried out at the expense of funds allocated within the framework of the State Assignment of the East-Siberian Institute of Medical and Ecological Research a grant from the Academic Council of Irkutsk National Research Technical University.

Conflict of Interest

The authors declare no conflicts of interest.

References

[1] Izmerov, N.F., Bukhtiyarov, I.V., Prokopenko, L.V. (2014). Implementation concept of the state policy aimed at preserving health of Russian working population up to the year 2020 and beyond. *Public Health and Life Environment, 9*, 4-8.

[2] Popova, A.Y. (2015). Working conditions and occupational morbidity in the Russian Federation. *Ekologiya cheloveka (Human Ecology)*, (3), 7-13.

[3] Izmerova, N.I., Istomin, A.V., Saarkopel, L.M., & Yatsyna, I.V. (2015). Topical problems and prospects of industrial medicine nowadays (according to materials of scientific and practical conferences of 2014). *Occupational medicine and industrial ecology*, (8), 43-47.

[4] Lavrentyeva, N.E., & Azovskova, T.A. (2012). Occupational allergic diseases of workers of chemical pharmaceutical industry and medical branch. *Health Officer, 9*, 032-035.

[5] Pankova, V.B. (2011). Evaluation of occupational allergic diseases of a respiratory tract. *Hygiene and sanitation, 1*, 51-54.

[6] Izmerova, N.I., Kouzmina, L.P., Tchistova, I.Ya., Ivtchenko, E.V., Tsidilkovskaya, E.S., & Kolyaskina, M.M. (2013). Occupational skin diseases as socioeconomic problem. *Occupational medicine and human ecology, 7*, 28-33.

[7] Tarasova, L.A., & Sorkina, N.S. (2003). Contemporary forms of occupational diseases. *Occupational medicine and human ecology*, *5*, 29-33.

[8] Rukavishnikov, V.S., Bodienkova, G.M., & Ushakova, O.V. (2010). Topical problems of occupational allergic diseases nowadays. *Occupational medicine and human ecology, 1*, 11-14.

[9] Pankov, V.A., Lakhman, O.L., Perezhogin, A.N., Tyutkina, G.A., Kuleshova, M.V., Smirnova, O.V. (2016). The dynamics of the occupational morbidity rate in Eastern Siberia. *Hygiene and sanitation, 95*(12), 1171-1175. http://doi.org/10.18821/0016-9900-2016-95-12-1171-1175.

[10] Bodienkova, G.M., Prokshets, O.V., & Tyutkina, G.A. (2003). Features of occupational allergic pathology in the Irkutsk region. *Materials of the II All-Russian Congress 'Profession and Health'. Irkutsk*, 169-171.

[11] Khotuleva, A.G., & Kuzmina, L.P. (2016). Biomarkers of system inflammation in pathogenesis of a sintropic of occupational bronchial asthma and metabolic syndrome. *Occupational medicine and human ecology, 7*, 39-43.

[12] Borisova, A.I., Idiyatullina, E.F., Gimranova, G.G., Bakirov, A.B., SHagalina, A.U., &

Masyagutova, L.M. (2018). Immunoglobulin E as a predictor of an early sensibilization of the workers exposed to industrial aerosols. *Health Officer, 4*, 22-25.

[13] Berest, I.E., & Tananakina, T.P. (2019). The role of microelement homeostasis in the pathogenesis of diseases of the upper respiratory tract. *Russian medical journal. Medical review, 3*(2), 27-29.

[14] Parakhonskiy, A.P. (2016). The effect of changes in the concentration of chemical elements on the pathogenesis of allergic diseases. Problems of the theory and practice of modern science. *Materials of the VI International Scientific Practical Conference.*

[15] Erina, I.A., & Sadretdinov, R.A. (2018). On the clinical and differential diagnosis of occupational dermatoses. *Synergy of sciences, 29*, 717-720.

[16] Malyugina, A.O., & Martynov, D.D. (2018). Allergic occupational diseases of workers. *Herald of modern research, 6.1*(21), 38-40.

[17] Nikiforova, G.A., Spiridonov, A.M., & Govryushin, Myu. (2017). Topical issues of prevention of occupational allergies. *Occupational medicine and industrial ecology, 9*, 138-139.

[18] Barkhina, T.G., Gushchin, MYu, Gusniyev, S.A., Polner, S.A., & Khayrullin, R.M. (2016). The role of macro and microelements in etiology and development of allergic diseases of respiratory ways (review article). *Morphological Newsletter, 24*(3), 99-106.

[19] Karimova, N.I., & Shamsiev, F.M. (2016). Clinical features of microelementoses at bronchial asthma. *Bulletin of I.K. Akhunbaev Kyrgyz State Medical Academy, 3*, 45-47.

[20] Ariaee, N., Farid, R., Shabestari, F., Shabestari, M., & Jabbari Azad, F. (2016). Trace elements status in sera of patients with allergic asthma. *Reports of Biochemistry & Molecular Biology, 5*(1), 20-25.

[21] Guo, C.H., Liu, P.J., Hsia, S., Chuang, C.J., & Chen, P.C. (2011). Role of certain trace minerals in oxidative stress, inflammation, CD4/CD8 lymphocyte ratios and lung function in asthmatic patients. *Annals of clinical biochemistry, 48*(4), 344-351. http://dx.doi.org/10.1258/acb.2011.010266

[22] Podkolzin, A.A., & Dontsov, V.I. (1994). *Immunity and minerals*. Moscow: Alamanda.

[23] Lavrova, A.E. (2000). The biological role of zinc is normal also at diseases. *Russian pediatrics journal, 3*, 42-47.

[24] Prokshets, O.V., Lisetskaya, L.G., & Budarina, L.A. (2004). The maintenance of essential minerals and antioxidant activity of lymphocytes at patients with occupational allergic pathology. *Materials of the II All-Russian Scientific and Practical Conference 'Compensatory-adaptive processes: fundamental, environmental and clinical aspects'. Novosibirsk*, 157-158.

[25] Rakitskij, V.N., & Yudina, T.V. (2005). Contemporary diagnostics problems: antioxidant and microelement organism status. *Bulletin of the Eastern Siberian Scientific Center of the Siberian Department of the Russian Academy of Medical Sciences, 2*, 222-227.

[26] *Methodical recommendations about spectral definition of heavy metals in biological materials and objects of the environment*. Moscow; 1986.

[27] Fletcher, R., Fletcher, S., & Vagner, E. (1998). *Clinical epidemiology*. Moscow: Media Sfera.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 485 - 493
Received 16 February 2021; Accepted 08 March 2021.

[28] Melikov, KCh., Nezhinskaya, G.I., Abyshev, A.Z., & Guseynov, S.N. (1993). The analysis of the activity of antioxidant system lymphocytes and of changes of permeability of erythrocyte membranes in patients with bronchial asthma and asthmatic bronchitis of professional genesis. *Immunology, 2*, 30–32.

[29] Kudrin, A.V., & Gromova, O.A. (2007). *Minerals in immunology and oncology*. Moscow: GEOTAR-Media.

[30] Skalnaya, M.G., & Skalny, A.V. (2015). Microelements: the biological role and significance for medical practice. Communication 1. Copper. *Biological, medical and pharmaceutical chemistry issues, 1*, 15-31.

[31] Oberlis, D., Skalny, A.V., Skalnaya, M.G., Nikonorov, A.A., & Nikonorova, E.A. (2015). Pathophysiology of microelementoses. Post 2. Zinc. *Patogenesis, 13*(4), 9-17.