*Медицинская иммунология
2023, Т. 25, № 5,
стр. 1165-1170*

*Краткие сообщения
Short communications*

*Medical Immunology (Russia)/
Meditsinskaya Immunologiya
2023, Vol. 25, №5, pp. 1165-1170*

ОСОБЕННОСТИ ВЗАИМОДЕЙСТВИЯ МЕДИ И КОБАЛЬТА, УЧАСТВУЮЩИХ В КРОВЕТВОРЕНИИ, И ВЛИЯНИЕ ИХ ДЕФИЦИТА НА РАЗВИТИЕ АНЕМИИ

Жиемуратова Г.К.

Институт иммунологии и геномики человека Академии наук Республики Узбекистан, г. Ташкент, Республика Узбекистан

Резюме. Одной из основных задач кроветворения является поддержание постоянного количественного и качественного состава отдельных компонентов и звеньев системы крови, что соответственно болезни крови можно рассматривать как нарушение закона клеточного равновесия. Физиологические механизмы адаптивной перестройки детского организма в экологически неблагоприятных условиях закономерно приводят к сдвигам элементного гомеостаза. Дефицит одного микроэлемента может привести к дисбалансу других микроэлементов.

Целью настоящего исследования является изучение роли и взаимодействия меди, кобальта и железа, участвующих в кроветворении, а также распространенность анемии среди детей, проживающих в регионе Приаралья.

Всего было обследовано 1120 детей и подростков. Был проведен клинический осмотр всех детей, с определением физического развития: выполнены антропометрические измерения и общепринятые лабораторные анализы. Для определения микроэлементного статуса исследованы волосы практически здоровых детей.

По результатам проведенных исследований выявлено, что у 78% детей наблюдается снижение гемоглобина. Показатели анемии у подростков был достоверно выше (в 2,5 раза), чем у детей младших возрастных групп ($p < 0,0001$).

Сравнительный анализ уровня эритроцитов и гемоглобина по основным показателям физического развития показала, что высокий рост положительно коррелирует с уровнем эритроцитов и гемоглобина.

В результате анализа микроэлементного состава волос у детей в регионе Приаралья, выявлены наиболее часто встречаемые гипомикроэлементозы. Общая частота микроэлементозов, обусловлена в основном дефицитом меди в 98,4% случаев (63), дефицитом кобальта в 92,1% (59), дефицитом цинка в 57,8% (37). Также проведено исследование не только содержания элементов, но и их соотношения. Выявлено повышенное соотношение Fe/Cu и Fe/Cu во всех возрастных группах. Дисбаланс микроэлементов, а также дефицит меди, кобальта, цинка способствуют развитию анемии у детей.

Полученные результаты показали, что анемия, выявляемая у детей, проживающих в регионе Приаралья, обусловлена не только снижением железа, но также снижением меди, кобальта, цинка, мар-

Адрес для переписки:

*Жиемуратова Гулпаршын Кошкинбаевна
Институт иммунологии и геномики человека Академии наук Республики Узбекистан
100060, Республика Узбекистан, г. Ташкент,
ул. Я. Гулямова, 74.
Тел.: +998 (61) 229-45-47; +998 (91) 301-72-44.
E-mail: gulparshin_76@mail.ru*

Address for correspondence:

*Gulparshin K. Jiemuratova
Institute of Immunology and Human Genomics,
Academy of Sciences of the Republic of Uzbekistan
74 Ya. Gulyamov St
Tashkent
100060 Republic of Uzbekistan
Phone: +998 (61) 229-45-47; +998 (91) 301-72-44.
E-mail: gulparshin_76@mail.ru*

Образец цитирования:

*Г.К. Жиемуратова «Особенности взаимодействия меди и кобальта, участвующих в кроветворении, и влияние их дефицита на развитие анемии» // Медицинская иммунология, 2023. Т. 25, № 5. С. 1165-1170.
doi: 10.15789/1563-0625-IBC-2810*

For citation:

*G.K. Jiemuratova "Interplay between copper and cobalt in hematopoiesis and the impact of their deficiency on anemia development", Medical Immunology (Russia)/Meditsinskaya Immunologiya, 2023, Vol. 25, no. 5, pp. 1165-1170.
doi: 10.15789/1563-0625-IBC-2810*

DOI: 10.15789/1563-0625-IBC-2810

ганца. Анализ волос на микроэлементы имеет свое значение в дифференциальной диагностике и лечении детей. Каждый из изученных микроэлементов, оказывает непосредственное влияние на состояние ребенка и возникновение различных заболеваний, в том числе анемий.

Ключевые слова: заболевание системы крови, анемия, железодефицитная анемия, дети, микроэлементы, основные микронутриенты гемопоэза

INTERPLAY BETWEEN COPPER AND COBALT IN HEMATOPOIESIS AND THE IMPACT OF THEIR DEFICIENCY ON ANEMIA DEVELOPMENT

Jiemuratova G.K.

Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan, Tashkent, Republic of Uzbekistan

Abstract. Hematopoiesis is a complex process that requires a specific set of blood components to function properly. Blood diseases can result from imbalances or deficiencies in these components. The body has physiological sensors that respond to environmental changes by maintaining elemental homeostasis. A deficiency in one micronutrient can lead to imbalances in others. The purpose of this study was to investigate the role and interaction of copper, cobalt, and iron in hematopoiesis and to determine the prevalence of anemia in children living in the Aral Sea region.

A total of 1120 children and adolescents were examined, and their physical development was measured using anthropometric measurements and laboratory tests. Hair samples were analyzed to determine the children's micronutrient status. The results revealed that 78% of the children had a decrease in hemoglobin, and anemia was more prevalent in adolescents. A correlation was found between high growth and increased levels of erythrocytes and hemoglobin. The study also identified the most common hypomicroelementoses in the Aral Sea region, including copper deficiency in 98.4% of cases, cobalt deficiency in 92.1%, and zinc deficiency in 57.8%.

The study also analyzed the ratio of trace elements, revealing an increased Fe/Cu and Fe/Cu ratio in all age groups. Imbalances and deficiencies in copper, cobalt, zinc, and manganese were found to contribute to the development of anemia in children. Hair analysis for trace elements was shown to be significant in the differential diagnosis and treatment of children with anemia.

In conclusion, the study highlights the importance of maintaining a proper balance of trace elements in hematopoiesis. Deficiencies in copper, cobalt, zinc, and manganese can contribute to anemia in children, and hair analysis can be used to diagnose and treat the condition. Further research is needed to better understand the role of trace elements in hematopoiesis and their impact on human health.

Keywords: blood system disease, anemia, iron deficiency anemia, children, trace elements, micronutrients of hematopoiesis

Introduction

One of the pivotal goals of hematopoiesis is to maintain the constant quantitative and qualitative composition of individual blood components and subsystems, which is predicated on the principle of kinetic regulation, whereby an equal number of cells are produced and undergo cell death per unit time. As such, hematologic disorders can be conceptualized as aberrations of cellular homeostasis [6].

Hematologic diseases are among the most prevalent maladies worldwide. Approximately one quarter of the global population, including young children and women, suffer from anemia, with iron-deficiency anemia (IDA) accounting for about 90% of all cases [5, 12]. In Karakalpakstan, the prevalence of anemia exceeds 40%, a level that has been identified as a grave health concern for the entire population, particularly children of all ages and women of reproductive age. This issue demands not only a medical approach, but also a social one that involves state-level interventions. Living conditions and health outcomes in the Aral Sea region are inextricably linked to the quantity and quality of available water resources. Research has revealed a correlation between the hardness (r = 0.40) and mineralization (r = 0.53) of drinking water and disease incidence in children. In this context, the physiological mechanisms that drive adaptive responses in children residing in ecologically adverse conditions inevitably lead to perturbations in elemental homeostasis [8, 9].

According to the available literature, nutritional imbalances among the population of the Aral Sea region may lead to the depletion of essential micronutrient reserves. In addition, the deficiency of one micronutrient may result in imbalances of other micronutrients. Furthermore, the inadequate supply of vital micronutrients can be attributed not only to their insufficient presence in food but also to the antagonistic effects of more toxic micronutrients [7, 8, 9].

Currently, anemia is viewed not only as a symptom of disease but also as a pathogenetic factor that exacerbates systemic damage in the organism. Nonetheless, many etiological and pathogenetic aspects of deficiency anemia remain unresolved to date.

The objective of the current study is to investigate the role and interaction of copper, cobalt, and iron in hematopoiesis, as well as the prevalence of anemia among children residing in the Aral Sea region.

Materials and methods

The study enrolled children and adolescents (from birth to 18 years of age) who underwent regular medical check-ups at their schools and resided in the Aral Sea region. A total of 1120 children were examined, all of whom were native inhabitants residing in the epicenter of the environmental crisis – the Republic of Karakalpakstan – and whose parents provided written consent for their participation in the study.

All children underwent a clinical examination, with assessments of their physical development including anthropometric measurements (height, weight, head and chest circumference) and standard laboratory analyses. The criteria for anemia were based on the reference values of hemoglobin levels proposed by the World Health Organization.

Hair samples were used for the assessment of the children's microelement status through neutron activation analysis. Hair is a convenient and non-invasive biological substrate for medical and biological research and offers several advantages compared to other biosubstrates. Hair analysis enables the evaluation of a child's microelement status, the determination of the state of individual organs and systems of the body based on this assessment, the degree of exposure to environmental factors, nutrition, and the development of methods to correct any identified deficiencies [1, 3, 10].

Hair samples from practically healthy children were examined to determine their micronutrient status. Of the total number of children examined, 64 aged between 1 and 18 years were selected for the study. All children were divided into four age groups: Group I comprised children from birth to 4 years, Group II comprised children from 4 to 8 years, Group III comprised children from 8 to 15 years, and Group IV comprised children from 15 to 18 years.

As a result of the multi-element determination of the composition of children's hair residing in the Aral Sea region, more than 20 elements were identified. This study focuses on the results of the analysis of hair samples for essential micronutrients, namely iron, cobalt, copper, and zinc.

The obtained data on the content of micronutrients in hair samples were compared with reference values for practically healthy children aged 1 to 18 years [1, 9]. Statistical processing of the obtained data was performed using Microsoft Excel 2007 and Statistica 6.0 software packages.

Results and discussion

According to the results of the conducted research, a decrease in hemoglobin was observed in 78% of the children, with an average of 97.8±1.6 g/L. Based on the obtained data, anemia of varying severity was detected in all age groups of children. Anemia was detected in 33.4% of children in group 1, 42.7% in group 2, 62.4% in group 3, and 72.2% in group 4.

The prevalence of anemia among adolescents was significantly higher (2.5 times) than in younger age groups of children ($p < 0.0001$).

According to the results of our study, the mean value of erythrocyte count in peripheral blood was 3.8±0.4 × 1012 cells/L. This laboratory parameter was significantly higher in children of the 1-2 age groups compared to those of the 3-4 age groups. Additionally, male children demonstrated higher levels of erythrocytes and hemoglobin compared to female children.

Further stratification of erythrocyte and hemoglobin levels by major indicators of physical development revealed a positive correlation between high height and erythrocyte/hemoglobin levels. Additionally, an increase in body mass and mass-height index values also showed a positive correlation with erythrocyte and hemoglobin parameters (Table 1).

However, this trend was observed only among 14-16-year-old children, especially boys. Both boys and girls under 14 years of age did not significantly differ in terms of their height and body weight from the average values for healthy children.

Comparative evaluation of weight and height indicators in children with anemia and healthy children showed that the greatest growth and body weight lag was observed in 14-year-old children. The height of healthy boys was 158.7±0.7 cm and girls 157.9±0.7 cm, while in children with anemia, these indicators did not exceed 153.5±0.7 and 151.4±0.3 cm, respectively ($p < 0.001$). In healthy

TABLE 1. COMPARATIVE ASSESSMENT OF AGE-RELATED DYNAMICS OF GROWTH AND BODY WEIGHT IN HEALTHY CHILDREN AND THOSE WITH ANEMIA LIVING IN THE ARAL SEA REGION

Age	Sex	Height, cm			Weight, kg		
		Children with anemia	Healthy children	p	Children with anemia	Healthy children	p
14	M	153.5±0.7	158.7±0.7	< 0.001	40.2±0.7	45.1±0.6	< 0.001
	F	151.4±0.4	157.9±0.7	< 0.001	40.1±0.4	47.2±0.7	< 0.001
15	M	162.6±0.2	166.1±0.6	< 0.001	46.5±0.2	50.3±0.6	< 0.001
	F	155.4±0.5	158.8±0.6	< 0.001	45.5±0.3	48.3±0.6	< 0.001
16	M	165.9±0.6	169.2±0.6	< 0.001	53.4±0.6	56.2±0.7	< 0.01
	F	156.7±0.4	159.5±0.5	< 0.001	48.5±0.7	51.1±05	< 0.01

Note. The anthropometric measurements of healthy children were used as a control in this study. p, significance of differences between data for healthy children and children with anemia. M, boys; F, girls.

children of the control group, the body weight in boys averaged 45.1±0.6 kg, and in girls 47.2±0.7 kg, while in children with anemia, it was respectively 40.2±0.7 and 40.1±0.4 kg ($p < 0.001$).

According to the results of recent studies, a correlation has been established between the frequency of verification of a decrease in the level of hemoglobin and erythrocytes and the environmental conditions of the region of residence. This may be explained by the peculiarities of the region's environment, diet, dietary traditions of the population, regional features of iron content in food products, and the absorption of this element in the body of adolescents.

The analysis of hair microelement composition in children living in the region of the Aral Sea revealed the most common hypomicroelementoses. The overall frequency of microelementoses was mainly due to a deficit of copper in 98.4% of cases (63), cobalt deficit in 92.1% (59), and zinc deficit in 57.8% (37). Only 29.6% of the examined children had iron deficiency (19), while the rest had iron levels within the reference values (20-30 μg/g). Table 2 shows the element content values for different age groups of children. As seen in the table, the most commonly encountered hypomicroelementoses are deficits of essential elements: Cu, Zn, Co, and Fe.

According to some authors [2, 5, 11], not only the content of elements but also their ratio should be taken into account. The results of the study showed that the ratios of elements have their peculiarities. The Fe/Cu coefficient was calculated for the examined children. An increased Fe/Cu ratio of more than 3 times was found in all age groups (Table 3).

It is widely known that many physiological and metabolic processes occurring in both children and adults are associated with free radical oxidation of lipids, proteins, and carbohydrates, in which iron plays an important role. According to N. A. Gres, a Fe/Cu ratio exceeding the optimal value of 0.9 indicates an increase in the amount of free radicals [11].

Moreover, the analysis of the Fe/Co coefficient also revealed a 2-4-fold increase in this ratio in each age group. Low values of this coefficient (< 440) indicate a predisposition of the body to thyroid dysfunction. N.A. Gres's data suggests that a decrease in iron content leads to the predominance of cobalt's influence on the metabolism of thyroid hormones, which can lead to disruptions in iodine exchange and the development of diffuse goiter.

Let us delve into the role of each element and its interaction with iron.

One of the essential elements for human health is copper. It is a constituent of vital enzymes involved in crucial respiratory and erythropoietic processes [13]. Copper serves as the primary activator of hemoglobin and participates in iron metabolism, promotes cel-

TABLE 2. CONTENT OF ELEMENTS IN THE HAIR OF CHILDREN LIVING IN THE ARAL SEA REGION IN ACCORDANCE WITH AGE GROUPS (mcg/g)

Element	Examined children				Norm range	
	I gr. 1-3 y. o. n = 16	II gr. 4-8 y. o. n = 14	III gr. 9-14 y. o. n = 16	IV gr. 15-18 y. o. n = 18	Min	Max
Fe	29.0±5.6	20.0±1.9	21.0±1.5	16.0±3.5	15	30
Co	0.0200±0.0027	0.0130±0.0034	0.0220±0.0044	0.0170±0.0034	0.02	0.11
Cu	6.90±0.97	6.60±0.89	7.5±1.0	7.2±1.0	10	15
Zn	83±14	120±73	120.0±8.1	170±18	150	250

TABLE 3. RATIO OF ESSENTIAL ELEMENTS IN CHILDREN OF DIFFERENT AGE GROUPS IN THE ARAL SEA REGION (mcg/g)

Proportion	Optimal	I gr. 1-3 y. o. n = 16	II gr. 4-8 y. o. n = 14	III gr. 9-14 y. o. n = 16	IV gr. 15-18 y. o. n = 18
Fe/Cu	0.9	3.50±0.65	3.40±0.88	3.90±0.61	3.00±0.63
Fe/Co	400	1286±133	1470±120	1620±195	1060±205

lular membrane stability, and facilitates iron transport from tissues to the bone marrow. Copper deficiency can impair erythro- and granulopoiesis, leading to the development of hypochromic anemia and neutropenia. Additionally, copper plays a crucial role in the functioning of the antioxidant system, being a component of superoxide dismutase. By activating cytochrome oxidase, it participates in the maturation and stimulation of reticulocytes and other hematopoietic cells [4].

The inadequate supply of copper results in poor iron absorption, leading to a reduced iron reserve in the depots and a decline in serum iron levels [11, 13]. Copper deficiency hampers the absorption and utilization of iron, thereby reducing the lifespan of erythrocytes. Previous studies have demonstrated the effectiveness of copper in treating anemia and investigated the potential mechanisms of copper's action on iron metabolism and its absorption in the intestine. These investigations continue today, utilizing modern molecular biology and genetics to further develop our understanding of these questions. In summary, there are copper-dependent factors in the hematopoietic system that promote iron absorption and erythropoiesis.

It is known that cobalt participates in many processes in the body, contributing to the production of erythrocytes in the bone marrow and better absorption of iron. The mass fraction of cobalt is 4.5% in vitamin B12. By activating hematopoiesis, cobalt regulates the synthesis of heme from protoporphyrin and iron, stimulates the production of erythropoietin, activates bone marrow functions, and accelerates the maturation of erythrocytes, preventing the development of anemia. In the liver of animals, more than 40% of cobalt is bound to protein fractions. Cobalt can form compounds with the amino acids histidine and cysteine. In case of cobalt deficiency, animals may develop anemia and hypokobaltosis.

It has been established that zinc deficiency leads to the development of zinc-deficient anemia (ZDA). Zinc affects the absorption of metals in the intestine and competes with copper. Zinc-dependent anemias can lead to taste distortion and muscle hypotonia. By influencing the processes of nucleic acid synthesis, zinc affects hematopoiesis, participates in the transport of carbon dioxide to the lungs, and is part of the enzyme carbonic anhydrase, which is present in erythrocytes [4].

It has been demonstrated that vitamin C facilitates the reduction of trivalent iron to divalent iron through copper-dependent ferrireductase enzymes, which subsequently enter enterocytes via manganese-dependent proteins and are transported into the bloodstream through the ferroportin protein. Iron plays a vital role in immune function, participating in the synthesis of immunoglobulins, collagen, and porphyrins, which can affect the quantity and functional properties of T lymphocytes. In normal conditions, approximately 30% of transferrin is saturated with iron. Iron is also involved in the functioning of non-specific defense factors, cellular immunity, and local immunity. Normal iron levels are necessary for proper phagocytosis and high natural killer activity. Iron deficiency in children can result in increased susceptibility to respiratory and gastrointestinal infections [5]. It has been established that children treated with iron supplements for anemia experience a reduced incidence of respiratory and intestinal infections. Iron maintains normal proliferation and mitotic activity of T lymphocytes through the "ribonucleotide-reductase" system. Iron-containing enzymes regulate the expression of major histocompatibility complex class II surface antigens on T lymphocytes. It has also been found that $Fe2^{+}$ ions, but not $Fe3^{+}$ ions, exhibit cytotoxic effects. In iron homeostasis, 9 copper-containing enzymes and 22 manganese-dependent proteins are involved [12].

The conducted study, analysis, and discussion of the obtained results have shown that anemia detected in children living in the Aral Sea region is caused not only by a decrease in iron but also by a decrease in copper, cobalt, zinc, and manganese. Hair analysis for trace elements has diagnostic and therapeutic value in children. Each of the studied trace elements has a direct impact on the child's health and the development of various diseases, including anemia.

Conclusion

Thus, the assessment of age-related physical development characteristics in children living in the environmentally disadvantaged region of the Aral Sea showed that it can be one of the sensitive, simplest, and most reliable criteria characterizing the state of organism development. Environmental factors in the region likely led to a delay in the pubertal age of the children. The slowdown in the pace of physical development in children is due to the general delay in their growth and the development of micronutrient deficiencies resulting from the negative impact of unfavorable environmental factors in the region. The obtained data emphasize the importance of the impact of the environment and the role of elemental status in the development of the child's body.

Imbalances in micronutrients, as well as deficiencies in copper, cobalt, and zinc, contribute to the development of anemia in children. Therefore, investigating the factors that provoke the development of anemia and studying possible ways to correct it is a relevant problem for Karakalpakstan and other countries worldwide.

References

1. Agadzhanyan N.A., Skalny A.V., Berezkina E.S., Demidov V.A., Grabeklis A.R., Skalnaya M.G. Reference values for chemical elements concentration in hair of adults in the republic of tatarstan. *Human Ecology, 2016, no. 4, pp. 38-44.* (In Russ.)
2. Belisheva N.K., Kozlova S.V., Tereshchenko P.S. The ratio of the essential elements in the hair in children living in different territories of the Kola North. *Proceedings of the Fersman Scientific Session, 2020, no. 17, pp. 38-42.* (In Russ.)
3. Danilova E.A., Osinskaya N.S., Khusniddinova S.Kh., Ahmedov Ya.A. The elemental content of hair as an indicator for natural and technogenic condition of Tashkent region. *Trace Elements in Medicine, 2020, no. 3 (21), pp. 24-32.* (In Russ.)
4. Filatov L.B. Copper deficiency as a hematological problem. *Clinical Oncohematology, 2010, no. 1.* (In Russ.)
5. Gombart A.F., Pierre A., Maggini S. A Review of micronutrients and the immune system-working in harmony to reduce the risk of infection. *Nutrients, 2020, Vol. 12, no. 1, 236.* doi: 10.3390/nu12010236.
6. He N., Zhang L., Cui J., Li Z. Bone marrow vascular niche: home for hematopoietic stem cells. *Bone Marrow Res., 2014, Vol. 2014, 128436.* doi: 10.1155/2014/128436.
7. Jiemuratova G.K., Ahmedjanova Z.I., Danilova E.A. Urunova D.M., Karimov D.A. Macro-microelements in the life of the body and their relationship with the immune system. *Journal of Theoretical and Clinical Medicine (Tashkent), 2020, no. 1, pp. 67-71.* (In Russ.)
8. Jiemuratova G.K., Ahmedjanova Z.I., Mambetkarimov G.A. Relationship between the quality of drinking water and the non-specific adaptive response of the body of children in the Aral Sea region. *Journal of Theoretical and Clinical Medicine (Tashkent), 2021, no. 4, pp. 85-87.* (In Russ.)
9. Khudainazarova S.R., Danilova E.A., Kuryazova Sh.M. Interrelation of health and hair elemental composition in children of prior school age in the Aral region. *Asian Journal of Pharmaceutical and Biological Research, 2022, Vol. 11, Iss. 1, pp. 38-45.*
10. Skalny A.V., Miroshnikov S.A., Notova S.V., Bolodurina I.P., Miroshnikov S.V., Alidzhanova I.E. Regional features of elemental homeostasis as an indicator of ecological and physiological adaptation. *Human Ecology, 2014, no. 9, pp. 14-17.* (In Russ.)
11. Tsirihova A.S., Minaev B.D., Butaev T.M. The evolution of metabolic relations of macro-and trance elements using the ration of their proportions in preschool educational institutions. *Modern Problems of Science and Education, 2016, no. 3.* (In Russ.) Available at: https://science-education.ru/ru/article/view?id=24481. (Date of application: April 21, 2023)
12. Vanoaica L., Richman L. Conditional deletion of ferritin h in mice reduces B and T lymphocyte populations. *PLoS One, 2014, Vol. 9, no. 2, e89270.* doi:10.1371/journal.pone.0089270.
13. Wu J., Ricker M., Muench J. Copper deficiency as cause of unexplained hematologic and neurologic deficits in patient with prior gastrointestinal surgery. *J. Am. Board Fam. Med., 2006, Vol. 19, no. 2, pp. 191-194.*

Автор:

Жиемуратова Г.К. *— к.м.н., старший научный сотрудник Института иммунологии и геномики человека Академии наук Республики Узбекистан, г. Ташкент, Республика Узбекистан*

Author:

Jiemuratova G.K., *PhD (Medicine), Senior Research Associate, Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan, Tashkent, Republic of Uzbekistan*

Поступила 14.04.2023
Отправлена на доработку 21.04.2023
Принята к печати 27.04.2023

Received 14.04.2023
Revision received 21.04.2023
Accepted 27.04.2023