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MICRONUTRIENT STATUS (VITAMINS A AND D) AND ITS EFFECT ON THE SEVERITY OF THE COURSE OF COVID-19 IN CHILDREN

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Summary

A strong immune response is important during recovery from COVID-19, and its status is influenced by several micronutrients. Vitamin D is important in regulating the immune response and protecting against respiratory infections. Vitamin A also has immunomodulatory effects, inhibiting viral replication and enhancing immune responses, thereby reducing morbidity and mortality from COVID-19.

***The aim of research** was to study the levels of vitamins A, D, and retinol-binding protein 4 in children with COVID-19, and their associations with the severity of the disease.*

***Material and Methods.** 112 children aged 1 month to 18 years with COVID-19 confirmed by polymerase chain reaction (PCR) in nasal swabs or by a positive serologic test (IgM and IgG or IgM). In all children, vitamin D levels were determined by the colorimetric enzyme-linked immunosorbent assay (ELISA) using the Monobind test system. Vitamin A and retinol binding protein 4 (RBP4) levels were determined by the colorimetric enzyme-linked immunosorbent assay (ELISA) using the Elabscience test system.*

Statistical analysis was performed using Stat Plus (its 95 % confidence interval (95 % CI) was calculated for the mean values, and the Kruskal-Wallis test (H-test) was used as the reliability criterion for checking the equality of the medians of several samples). The level of statistical significance was set at $P<0.05$).

The study was conducted in accordance with the rules of patient safety and ethical principles of scientific medical research involving human subjects (2000). The permission to conduct this study was granted by the Bioethics Commission (Protocol No. 73, dated April 3, 2023). The parents (legal representatives) of the patients gave their written consent to the conduct of this study.

This study is a fragment of research work «Optimizing the diagnosis of clinical and pathogenetic characteristics of the COVID-19 coronavirus infection in children with comorbid pathology and treatment features» (state registration No. 0123U100064, 2023-2025).

***Results.** The mean age of the children was (7.04±5.75) years (95 % CI 5.96-8.12). According to the severity of the disease, 57 children (50.89 %) had a mild course, 43 children (38.39 %) had a moderate course, and 12 children (10.72 %) had a severe course. The concentration of vitamin D in children with mild course of COVID-19 was 30.91 ng/ml, in children with moderate course – 29.10 ng/ml, in children with severe course – 22.42 ng/ml ($P<0.05$). The level of vitamin A also varied in children with different severity of the disease: in mild COVID-19 it was 456.10 ng/ml, in moderate – 347.30 ng/ml, and in severe – 242.90 ng/ ml ($P<0.001$). At the same time, the level of retinol binding protein 4 was 30.66 ng/ml in mild disease, 33.07 ng/ml in moderate disease and 23.28 ng/ml in severe disease.*

***Conclusions.** Children with moderate and severe COVID-19 have significantly lower levels of vitamins A, D, and RBP4 compared to uninfected individuals. Vitamin A and RBP4 levels were age-dependent, and vitamin D levels did not show age-related patterns. Lower levels of vitamins A and D are associated with higher levels of pro-inflammatory markers – CRP, leukocytes and ESR.*

***Key words:** COVID-19; Children; Vitamin D; Vitamin A; Retinol-binding protein 4.*

Introduction

COVID-19, caused by the SARS-CoV-2 virus, has now become the cause of a large-scale outbreak of the disease with a diverse clinical picture, severe complications and high mortality [1].

In the publications, researchers point out that the proportion of children among the sick is much lower than that of adults. Children represent 1-11 % of patients with confirmed disease [2,3]. Children acquire a new infection but tolerate it more easily than adults, and complications and adverse effects are less frequent [4,5].

Since the beginning of the coronavirus pandemic, the scientific community has been urgently seeking reliable biomarkers of disease progression for the early identification of high-risk patients [1]. Due to the rapid spread of the disease, there is a need to stratify patients into risk categories immediately after diagnosis to ensure optimal allocation of resources [6]. Reliable biomarkers would be useful for screening, clinical management, and prevention of serious complications [1].

Studies confirm that a sustained immune response is critical in the recovery process from COVID-19 [7]. A large body of knowledge has also accumulated on the influence of various micronutrients on the state of the immune system. In addition, micronutrients are involved in the coordination of innate and adaptive immune responses to viral infections, particularly in the regulation of pro- and anti-inflammatory responses in the human body [8]. In addition, an insufficient amount of trace elements not only weakens the immune system in the fight against viral infections, but also contributes to the emergence of more virulent strains due to changes in the genetic composition of the viral genome [9]. Adequate immunity requires a constant supply of nutrients. Vitamins and microelements have a significant, often synergistic, effect at each stage of immune protection [10].

Vitamin A plays an immunoregulatory role in cellular and humoral immune responses [11]. It induces an immediate innate antiviral immune response in infected cells [12]. Vitamin A inhibits viral replication, promotes the immune response, and reduces the morbidity and mortality of some viral infections [13]. Retinol-binding protein (RBP4) is synthesized in the liver and is responsible for binding retinol and transporting it to the organs.

Vitamin D has many important functions, not only in phosphorus-calcium metabolism, but also in immunity and antimicrobial response. It has important effects on the host immune system, modulating both innate and adaptive immunity and regulating the inflammatory cascade [14,15]. Vitamin D deficiency is known to be the major risk factor for the development of infectious diseases [13,15-16]. Vitamin D deficiency has been shown to increase the morbidity and severity of COVID-19 [17].

The purpose of this study was to analyze the levels of vitamins A, D, and retinol-binding protein 4 in children with COVID-19, evaluate their indicators depending on the severity of the disease and study the interrelationship between vitamin level and pro-inflammatory markers.

Material and Methods. 112 children aged 1 month to 18 years with COVID-19 confirmed by polymerase chain reaction (PCR) in nasal swabs or/and positive serological test (IgM and IgG, or IgM) who were in the infectious disease department of the Ternopil City Children's Hospital from March 2021 to May 2023. Blood samples were taken on the first day after hospital admission.

According to the severity of the course of the disease, 3 groups of patients were formed: Group I – children with a mild course of the disease, which was diagnosed in 57 children, Group II – 43 children – with a moderate course, Group III – 12 children with a severe course (Table 1).

The degree of severity of the course of COVID-19 was determined according to medical recommendations [18] – the presence and severity of such clinical symptoms as cough, weakness, sore throat, shortness of breath during physical exertion, indicators of body temperature and respiratory rate, confirmation of pneumonia in a child (using computerized tomography of the lungs), indicators of blood oxygen saturation (SpO2), the level of C-reactive protein in blood serum.

The control group included 23 practically healthy children, aged from 1 month to 18 years, without clinical signs or anamnestic data that would indicate the presence of acute or chronic infectious and/or somatic pathology.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). *The Bioethics Commission of I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine (Protocol No 73 dated April 03, 2023) approved the study.* Individual informed consent for this analysis was obtained from all children's caregivers.

In all 135 children, from the study and control groups, the levels of vitamins A, D, and retinol-binding protein 4 (RBP4) were determined in the laboratory by the colorimetric method of enzyme-linked immunosorbent assay (ELISA) using the Elabscience test system (for vitamin A and RBP4) and Monobind (for vitamin D).

A sufficient level of vitamin A was considered to be ≥300 ng/ml, vitamin A insufficiency – 200~300 ng/ml, a slight deficiency – 100~200 ng/ml, and a deficiency – < 100 ng/ml [19].

A sufficient level of vitamin D was considered to be 30-100 ng/ml, a deficiency of vitamin D – 29-20 ng/ml, and a deficiency – <20 ng/ml [20].

Statistical analysis was performed using Stat Plus (their 95 % confidence interval (95 % CI) was calculated for the average values, and the reliability criterion for checking the equality of the medians of several samples is the Kruskal-Wallis test (H-test). The level of statistical significance was taken to be $P<0.05$).

This study is a fragment of research work «Optimizing the diagnosis of clinical and pathogenetic characteristics of the COVID-19 coronavirus infection in children with comorbid pathology and treatment features» (state registration No. 0123U100064, 2023-2025).

Results and discussion

The mean age of the children studied was (7.04±5.75) years (95 % CI 5.96-8.12). The ratio of boys to girls was 1:1.15.

Based on the COVID-19 severity, the children were divided into three groups – 57 children (50.89 %) had a mild course of the disease and the mean age in this group was (6.73±5.77) years (95 % CI 5.23-8.23), 43 children (38.39 %) had a moderate course of the disease with the mean age (7. 9±5.76) years (95 % CI 6.16-9.64), and 12 children (10.72 %) had a severe course and the mean age in this group was (7.31±6.22) years (95 % CI 3.36-11.26), the mean age of the control group was (6.92±5.72) years (95 % CI 4.45-9.39).

The vitamin A level in children with mild disease was 456.10 ng/mL, which was significantly higher than that in the moderate (347.30 ng/mL) and severe (242.90 ng/mL) groups (P<0.05) (Table 1). Patients with moderate and severe SARS-CoV-2 infection had significantly lower vitamin A levels compared with non-infected persons (P<0.05). At the same time, vitamin A levels did not differ between patients with mild COVID-19 and the control group (P>0.05).

The level of retinol binding protein 4 was 30.66 ng/ml in mild, 33.07 ng/ml in moderate and 23.28 ng/ml in severe cases. No significant differences were found between the groups with COVID-19 (p>0.05) (Table 1). At the same time, RBP4 was significantly lower in patients with severe COVID-19 compared to healthy subjects (P<0.05).

The concentration of vitamin D in children with mild course of COVID-19 was 30.91 ng/ml, in children with moderate course – 29.10 ng/ml, in children with severe course – 22.42 ng/ml (Table 1). The vitamin D level in the control group was significantly higher than in patients with moderate and severe course (P<0.05).

The study showed that most children with mild disease (85.96 %) and moderate disease (67.44 %) had sufficient vitamin A. In the case of severe COVID-19, 58.00 % of the children had vitamin A insufficiency. Vitamin A deficiency was significantly more frequent in patients with severe COVID-19 (25.00 %) compared to mild (12.28 %) and moderate (6.98 %) disease severity (Table 2).

Table 1

The concentration of vitamins varied according to the severity of the course of the disease

Groups	Vitamin A, ng/ml	Retinol-binding protein 4, ng/ml	Vitamin D, ng/ml
Mild COVID-19 course (1)	456.10 (394.00; 566.00)	30.66 (26.74; 37.12)	30.91 (21.50; 42.45)
Moderate COVID-19 course (2)	347.30 (279.60; 503.10)	33.07 (26.73; 43.13)	29.10 (21.25; 37.68)
Severe COVID-19 course (3)	242.90 (203.25; 272.55)	23.28 (18.09; 26.81)	22.42 (18.99; 30.50)
The control group (4)	487.00 (430.50; 653.90)	37.38 (31.94; 43.59)	37.90 (34.60; 43.25)
Kruskal-Wallis test	H=30.18; P <0.001*	H=12.02; P=0.007*	H=14.34; P=0.003*
P<0.05*	P_{1-2}, P_{1-3}, P_{2-4}, P_{3-4}	P_{3-4}	P_{2-4}, P_{3-4}

*Note. * – statistically significant result.*

Table 2

Levels of vitamin A and the disease severity

Vitamin A level	COVID-19 groups						The control group	
	A mild course		A moderate course		A severe course			
	n	%	n	%	n	%	n	%
Sufficient level	49	85.96	29	67.44	2	16.67	23	100.00
Insufficiency	1	1.75	11	25.58	7	58.33	0	0
Mild deficiency	7	12.28	2	4.65	3	25.00	0	0
Deficiency	0	0	1	2.33	0	0	0	0

Note 1. χ^2=47.85; P<0.001.*

*Note 2. * – statistically significant result.*

Most children with a mild course of COVID-19 (55.56 %) and with a moderate course (42.86 %) had a sufficient level of vitamin D. Vitamin D deficiency was more typical for children with a severe disease course (41.67 %) (Table 3).

Table 3

Vitamin D levels and disease severity

The level of vitamin D	COVID-19 groups						The control group	
	A mild course		A moderate course		A severe course			
	n	%	n	%	n	%	n	%
Sufficient level	20	55.56	12	42.86	3	25.00	13	86.67
Insufficiency	9	25.00	11	39.29	4	33.33	2	13.33
Deficiency	7	19.44	5	17.86	5	41.67	0	0

Note 1. χ^2=14.41; P=0.013.*

*Note 2. * – statistically significant result.*

The research revealed that vitamin A and D deficiencies were significantly more common in children with coronavirus infection compared to healthy children who made up the control group (P<0.05) (Table 2 and Table 3).

A mild course of the disease was found in 13 children (22.81 %) aged less than 1 year (group I), 25 children (43.86 %) aged 1 to 10 years (group II), and 19 children (33.33 %) aged over 10 years (group III). In the group of children with moderate course of the disease, there were 5 children (9.30 %) who were infants, 24 children (55.81 %) aged 1 to 10 years, and 15 children (34.88 %) over 10 years. In the group of children with severe disease, there were 2 children (16.67 %) less than 1 year of age, 6 children (50.00 %) 1 to 10 years of age, and 4 children (33.33 %) over 10 years of age (Table 4). There were no significant age differences between the groups of children with different severity of coronavirus infection (χ2=3.37; P=0.497).

Table 4

Age groups of children and the severity of the disease

Age groups	A mild course		A moderate course		A severe course	
	n	%	n	%	n	%
< 1 year	13	22.81	4	9.30	2	16.67
1-10 years	25	43.86	24	55.81	6	50.00
>10 years	19	33.33	15	34.88	4	33.33

Note 1. χ^2=3.37; P=0.497.

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It was found that children of the older age group (>10 years) have a lower level of vitamin A – 390.85 ng/ml compared to younger patients – 498.40 ng/ml (P<0.05). It should be noted that the level of RBP4 increases with the age of the child – in children under 1 year – 25.09 ng/ml, in children 1-10 years – 31.13 ng/ml, and in children over 10 years – 33.26 ng/ml. At the same time, no age-related differences in vitamin D concentration were found (Table 5).

According to the study results, the content of vitamins A and D, as well as RBP4, did not differ between boys and girls (*P*>0.05) (Table 6).

It has been established that vitamin A deficiency is associated with higher levels of CRP, ESR, and leukocytosis (Table 7). At the same time, an increase in the value of ESR is characteristic of patients with vitamin D deficiency (Table 7).

Table 5

Age differences and the concentration of vitamins A, D and RBP4

Age group	Vitamin A, ng/ml	Retinol-binding protein 4, ng/ml	Vitamin D, ng/ml
< 1 year	498.40 (383.90; 566.0)	25.09 (19.34; 30.66)	32.83 (19.42; 45.35)
1-10 years	398.00 (263.30; 532.70)	31.13 (26.45; 40.68)	29.16 (22.19; 37.09)
>10 years	390.85 (241.80; 507.40)	33.26 (26.84; 43.06)	25.60 (21.16; 32.26)
Kruskal-Wallis test	H=5.78; P=0.045*	H=7.14; P=0.028*	H=1.96; P=0.374
P<0.05*	P_{1-3}	P_{1-3}	–

*Note. * – statistically significant result.*

Table 6

Gender differences and the concentration of vitamins A, D and RBP4

Gender	Vitamin A, ng/ml	Retinol-binding protein 4, ng/ml	Vitamin D, ng/ml
Boys	423.65 (285.15; 533.95)	29.62 (22.39; 36.82)	30.90 (21.56; 36.81)
Girls	395.05 (250.10; 513.45)	31.08 (25.16; 40.68)	25.64 (19.71; 34.49)

Note. P>0.05.

Table 7

Levels of CRP, leukocytes, neutrophils, lymphocytes, and ESR depending on the micronutrient status (vitamins A and D) of the patients

Indicator	Vitamin A			Vitamin D		
	Sufficient level	Insufficiency	Deficiency	Sufficient level	Insufficiency	Deficiency
CRP, mg/l	7.35 (4.15; 14.05)	13.80 (9.40; 26.60)	14.96 (7.05; 33.80)	8.90 (4.50; 24.00)	7.40 (5.50; 21.90)	15.09 (9.45; 32.75)
	H=8.68; P=0.013*; $P_{1-2, 1-3}$<0.05*			H=2.96; P=0.228		
Leukocytes, 10^9/l	7.23 (4.40; 9.58)	7.71 (4.00; 12.90)	11.50 (7.87; 15.32)	7.83 (5.20; 10.24)	7.39 (4.42; 12.90)	9.88 (6.79; 15.56)
	H=7.80; P=0.020*, P_{1-3}<0.05*			H=2.49; P=0.288		
Neutrophils, %	55.00 (38.00; 67.50)	59.00 (45.00; 75.00)	64.00 (48.00; 70.00)	54.00 (36.00; 60.00)	64.00 (39.00; 75.00)	66.00 (41.00; 83.00)
	H=1.30; P=0.522			H=3.46; P=0.177		
Lymphocytes, %	38.00 (25.00; 49.00)	23.50 (18.00; 45.00)	26.00 (21.00; 40.00)	38.00 (25.20; 49.00)	22.50 (18.00; 40.00)	26.00 (17.00; 47.00)
	H=4.13; P=0.127			H=5.08; P=0.079		
ESR, mm/h	6.00 (4.00; 12.00)	17.00 (8.00; 21.00)	21.00 (5.00; 27.00)	6.00 (5.00; 16.00)	8.00 (6.00; 19.00)	17.00 (12.00; 22.00)
	H=14.92; P<0.001*, $P_{1-2, 1-3}$<0.05*			H=7.00; P=0.030*; P_{1-3}<0.05*		

*Note. * – statistically significant result.*

The SARS-CoV-2 virus affects human immunity, i.e. the severity of the infection depends on the immune competence [21]. It is known that a change in the status of trace elements in the body can influence the course of immunological processes [22]. Clinical studies indicate the vital role of trace elements in the prevention and treatment of viral infections [23].

Vitamins A and D have received particular attention in recent years, as these vitamins have been shown to play unexpected key roles in the immune response [17].

Vitamins A and D play important roles in the immune response, and deficiency of each is associated with more severe disease and complications in children with respiratory infections [17, 24-25]. Low vitamin D levels are associated with an increased incidence of upper respiratory tract infections [24]. Therefore, in our study, children with mild disease had higher levels of vitamins A and D than children with moderate or severe disease.

In addition, higher levels of vitamins A and D have been shown to reduce the body's inflammatory response to infectious diseases [17, 18]. In our study, we observed higher levels of ESR and C-reactive protein in patients with lower levels of vitamin A.

Vitamins A and D interact, cross-regulate, and affect numerous organ systems, including the lungs and their epithelial cells [17, 26]. Low levels of vitamins D and A are significantly associated with higher rates of intensive care unit admission and mechanical ventilation [27]. These findings are consistent with the results of our study, where children with higher levels of these vitamins did not require intensive care, whereas lower levels of vitamins A and D were observed in severe cases of COVID-19 that required treatment in the intensive care unit.

Conclusions

In our study, both insufficiency and deficiency of vitamins A and D were more frequently observed in children with coronavirus infection compared to healthy children. The levels of vitamin A were related to the severity of the disease: sufficient levels of vitamin A were more typical for a mild course of COVID-19, whereas insufficiency and deficiency were more typical for a moderate and severe course. Vitamin A levels were higher in children with mild disease compared to groups of children with moderate and severe COVID-19.

Research has shown that vitamin D insufficiency and deficiency are most commonly associated with the severe course of COVID-19. The frequency of adequate vitamin D levels is significantly lower in patients with severe COVID-19 compared to healthy children as well as children with mild disease severity.

Study results showed that lower levels of vitamins A and D are associated with higher levels of pro-inflammatory markers – CRP, leukocytes and ESR.

Concentrations of vitamins A, D, and retinol-binding protein 4 did not differ by sex. Vitamin A levels were significantly lower in children over 10 years of age than in infants. RBP4 levels increased with age. Vitamin D levels did not show age-related patterns.

The presence of micronutrient deficiencies in infected individuals and the effect of micronutrient supplementation on overall disease outcome may be of great interest in the use of micronutrients for the prevention and/or treatment of infectious diseases such as COVID-19.

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МІКРОНУТРІЄНТНИЙ СТАТУС (ВІТАМІНИ А ТА D) ТА ЙОГО ВПЛИВ НА ВАЖКІСТЬ ПЕРЕБІГУ COVID-19 У ДІТЕЙ

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Резюме.

Під час одужання від COVID-19 важлива сильна імунна відповідь, на стан якої впливають різноманітні мікроелементи. Вітамін D важливий для регуляції імунної відповіді та захисту від респіраторних інфекцій. Вітамін А також має імуномодулюючу дію, пригнічуючи реплікацію вірусу та посилюючи імунну відповідь, тим самим знижуючи захворюваність і смертність від COVID-19.

Метою дослідження було вивчити рівні вітамінів А, D і ретинолзв'язуючого білка 4 у дітей з COVID-19, а також їх зв'язок із тяжкістю захворювання.

Матеріал і методи дослідження: обстежено 112 дітей віком від 1 місяця до 18 років із COVID-19, підтвердженим методом полімеразної ланцюгової реакції (ПЛР) у мазках з носа або позитивним серологічним тестом (IgM та IgG або IgM). У всіх дітей визначали рівень вітаміну D колориметричним методом імуноферментного аналізу (ІФА) з використанням тест-системи Monobind. Рівні вітаміну А та ретинолзв'язуючого білка 4 (RBP4) визначали колориметричним методом імуноферментного аналізу (ELISA) з використанням тест-системи Elabscience.

Комісія з біоетики Тернопільського національного медичного університету імені І. Горбачевського МОЗ України (протокол № 73 від 03.04.2023) схвалила дослідження. Індивідуальна інформована згода на цей аналіз була отримана від усіх опікунів дітей.

Статистичний аналіз здійснювався за допомогою програми «Stat Plus» (під час статистичної обробки отриманих даних для середніх значень розраховано їх 95 % довірчий інтервал (95 % ДІ), а критерієм достовірності для перевірки рівності медіан кількох вибірок є критерій Крускала-Уолліса (Н-критерій). Рівень статистичної значущості прийнято $P<0,05$).

Дане дослідження є фрагментом науково- дослідної роботи «Оптимізація діагностики клініко-патогенетичних характеристик коронавірусної інфекції COVID-19 у дітей з коморбідною патологією та особливості лікування « (державна реєстрація No 0123U100064, 2023-2025 pp).

Результати дослідження. Середній вік дітей становив (7,04 ± 5,75) років (95 % ДІ 5,96-8,12). За ступенем тяжкості у 57 дітей (50,89 %) перебіг захворювання був легким, у 43 дітей (38,39 %) – середньої тяжкості, у 12 дітей (10,72 %) – тяжкий. Концентрація вітаміну D у дітей із легким перебігом COVID-19 становила 30,91 нг/мл; при середньотяжкому перебігу – 29,10 нг/мл; у дітей із тяжким перебігом – 22,42 нг/мл ($P < 0,05$). Рівень вітаміну А також різнився у дітей з різним ступенем тяжкості захворювання: при легкому перебігу COVID-19 він становив 456,10 нг/мл; 347,30 нг/мл при середньому ступені тяжкості та 242,90 нг/мл при тяжкому перебігу ($P < 0,001$). При цьому рівень ретинолзв'язуючого білка 4 становив 30,66 нг/мл при легкому перебігу; 33,07 нг/мл при середньому ступені тяжкості захворювання; і 23,28 нг/мл при тяжкому перебігу.

Висновки: Діти із середньотяжким та важким перебігом COVID-19 мають значно нижчі рівні вітамінів А, D і RBP4 порівняно з неінфікованими людьми. Рівні вітаміну А і RBP4 залежали від віку, а рівень вітаміну D не мав вікових закономірностей. Нижчий рівень вітамінів А і D пов'язаний з більш високим рівнем прозапальних маркерів – СРБ, лейкоцитів і ШОЕ.

Ключові слова: COVID-19; діти; вітамін D; вітамін А; ретинолзв'язуючий білок 4.

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