ХОЛЕКАЛЬЦИФЕРОЛ В РОЛИ СРЕДСТВА НЕСПЕЦИФИЧЕСКОЙ ИММУНОПРОФИЛАКТИКИ COVID-19

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Резюме. Актуальным направлением научного поиска последних лет стало исследование иммунобиологических свойств витамина D. Целью данной работы стал анализ результатов перорального применения холекальциферола в целях предупреждения инфицирования вирусом SARS-CoV-2 в первую волну пандемии COVID-19. Исследование выполнено в период с 07 октября по 29 декабря 2020 года, когда отсутствовали иммунобиологические препараты для специфической профилактики COVID-19. Общее количество респондентов составило 73 человека, все однократно перенесли новую коронавирусную инфекцию. Этиологическая диагностика заболевания включала молекулярно-генетическое тестирование полученных общепринятым способом образцов двух локализаций (носоглотка, ротоглотка). Концентрация антител к вирусу определена в среднем через 2 месяца после болезни с использованием набора реагентов SARS-CoV-2-IgG количественный-ИФА-Бест (АО «Вектор-Бест», Россия). Ориентировочную оценку концентрации IgM осуществляли с использованием набора SARS-CoV-2-IgM-ИФА-Бест того же производителя. Среди участников исследования были такие, кто в целях профилактики инфицирования использовал иммунобиологические препараты (риамиловир, умифеновира гидрохлорида моногидрат, интерферон альфа-2b человеческий рекомбинантный, ацетат цинка, витамин С), в частности 28 человек (38,4%) принимали холекальциферол (группа № 1) и 45 человек (61,6%) не использовали его (группа № 2). Статистическая обработка полученных данных произведена с использованием статистического пакета STATISTICA v.12.5.192.5 (StatSoft, Inc., USA). Применен анализ базовых статистик, Linear Discriminant Analysis, Kolmogorov–Smirnov test, Chi-Square test, Wald–Wolfowitz Runs Test, Kruskal–Wallis test.

Выявлены отличия в частоте развития респираторного дистресс-синдрома двух изученных групп: у пациентов, принимавших холекальциферол синдром не развивался совсем, в группе № 2 он регистрировался в 20,0% случаев (Chi-Square = 5,242, p = 0,02). Помимо этого, у пациентов группы № 1 концентрация IgG через 2 месяца после болезни была в 3,8 раз выше значений в группе № 2 (Chi-Square = 9,268, p = 0,003). Сходные отличия выявлены и для уровня IgM (Wilks' Lambda: 0,659 approx. F (7,32) = 2,367 p < 0,045). Было известно, что в обеих группах присутствовали респонденты, применявшие в профилактических целях и другие иммуноактивные вещества. В первой группе таких было 18 человек (24,7% от всех), во второй – 13 человек (17,8% от всех). Установлено, что те, кто использовал другие иммуноактивные вещества и не принимал витамин D перенесли заболевание легче всех остальных. Следующими по степени тяжести перенесенной инфекции были респонденты,

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не использовавшие никаких иммунопрофилактических средств. Респонденты, принимавшие холекальциферол, преимущественно оценили тяжесть инфекции как среднюю. Участники исследования, принимавшие и витамин D и использовавшие другие средства профилактики, наиболее тяжело перенесли COVID-19. Респонденты, принимавшие холекальциферол, чаще других сообщали о длительно сохраняющейся утомляемости, об обострении хронических и появлении новых заболеваний (гипертоническая болезнь, кардиалгия, бронхиальная астма, аллергия, снижение остроты зрения), впервые появившихся мышечных, суставных и позвоночных болях. Феномен артралгий и других поражений крупных суставов при COVID-19 описывался нами ранее. В исследованиях других авторов также сообщается о частых жалобах на повышенную утомляемость и боли в суставах. При этом роль витамина D рассматривается исключительно с позиции его недостаточности при новой коронавирусной инфекции и его потенциальной роли в ингибировании гипервоспалительных реакций, а также ускорении процесса заживления пораженных участков, особенно в легочной ткани.

Установлено, что прием витамина D не влиял на частоту возникновения лихорадочного состояния, частоту развития пневмонии легких, объем поражения тканей легких (на основании данных компьютерной томографии), длительность госпитализации и заболевания в целом, а также не предотвращал развитие аносмии и дисгевзии. Использование витамина D, как протективного средства для предотвращения инфицирования вирусом SARS-CoV-2, оказало влияние на снижение частоты / предотвращение случаев респираторного дистресс-синдрома в процессе заболевания. Также у принимавших витамин D зафиксировано увеличение образования IgG к вирусу SARS-CoV-2 через 2 месяца после инфицирования 3,8 раза выше значений, зарегистрированных у респондентов, не принимавших колекальциферол. Участники, принимавшие холекальциферол, переносили инфекцию тяжелее, особенно, если использовали еще какие-либо протективные вещества. Также при превентивном приеме витамина D после COVID-19 дольше сохранялась повышенная утомляемость, чаще сообщалось о появлении новых и активации хронических заболеваний и впервые появившихся мышечных, суставных и позвоночных болях, что соотносится с полученными нами ранее данными.

Ключевые слова: COVID-19, холекальциферол, риамиловир, умифеновира гидрохлорида моногидрат, аскорбиновая кислота, цинк, IFNα-2b человеческий рекомбинантный, сустав, позвоночник

CHOLECALCIFEROL AS A MEANS OF NONSPECIFIC IMMUNOPROPHYLAXIS AGAINST COVID-19

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Abstract. The current direction of scientific research in recent years has been the study of the immunobiological properties of vitamin D. The purpose of this work was to analyze the results of oral administration of cholecalciferol in order to prevent infection with the SARS-CoV-2 virus in the first wave of the COVID-19 pandemic. The study was performed in the period from October 07 to December 29, 2020, when there were no immunobiological drugs for specific prevention of COVID-19. The total number of respondents was 73 people; all had been ill with coronavirus only once. The etiological diagnosis of the disease included molecular genetic testing of samples of two localizations obtained by the conventional method (nasopharynx, oropharynx). The concentration of antibodies to the virus was determined on average 2 months after the disease using a set of reagents SARS-CoV-2-IgG quantitative-ELISA-Best (JSC Vector-Best, Russia). An approximate assessment of IgM concentration was carried out using a set of SARS-CoV-2-IgM-ELISA-Best from the same manufacturer. Among the study participants were those who used immunobiological drugs for the prevention of infection (riamilovir, umifenovir hydrochloride monohydrate, human recombinant interferon alpha-2b, zinc acetate, vitamin C). In particular, 28 people (38.4%) took cholecalciferol (group No. 1) and 45 people (61.6%) did not use this (group No. 2). Statistical processing of the obtained data was performed using the statistical package STATISTICA v.12.5.192.5 (StatSoft, Inc., USA). We applied the analysis of basic statistics, Linear Discriminant Analysis, Kolmogorov–Smirnov test, Chi-Square test, Wald–Wolfowitz Runs Test, Kruskal–Wallis test.

Differences in the incidence of respiratory distress syndrome of the two studied groups were revealed: in patients taking cholecalciferol, the syndrome did not develop at all; in group No. 2, it was registered in 20.0% of cases (Chi-Square = 5.242, p = 0.02). In addition, in patients of group No. 1, the concentration of IgG 2 months after the disease was 3.8 times higher than the values in group No. 2 (Chi-Square = 9.268, p = 0.003).

Similar differences were found for the IgM level (Wilks' Lambda: 0.659 approx. F (7.32) = 2.367 p < 0.045). It was known that in both groups there were respondents who used other immuno-active substances for preventive purposes. In the first group there were 18 people (24.7% of all); in the second, there were 13 people (17.8% of all). It was found that those who used other immuno-active substances and did not take vitamin D suffered the disease more easily than everyone else. The respondents who did not use any immunoprophylactic agents were the next in terms of the severity of the infection. The respondents who took cholecalciferol mainly assessed the severity of the infection as average. The study participants who took both vitamin D and used other means of prevention suffered the most from COVID-19. Respondents who took cholecalciferol more often than others reported long-term fatigue, exacerbation of chronic and the appearance of new diseases (hypertension, cardialgia, bronchial asthma, allergies, decreased visual acuity), muscle, joint and vertebral pains that appeared for the first time. The phenomenon of arthralgia and other lesions of large joints in COVID-19 was described by us earlier. Studies by other authors also report frequent complaints of increased fatigue and joint pain. At the same time, the role of vitamin D is considered exclusively from the standpoint of vitamin deficiency in a new coronavirus infection and its potential role in inhibiting hyperinflammatory reactions, as well as accelerating the healing process of affected areas, especially in lung tissue.

It was found that vitamin D intake did not affect the incidence of fever, the incidence of pneumonia, the volume of lung tissue damage (based on computed tomography data), the duration of hospitalization and the disease as a whole, and also did not prevent the development of anosmia and dysgeusia. The use of vitamin D as a protective agent to prevent infection with the SARS-CoV-2 virus has had an impact on reducing the frequency/prevention of cases of respiratory distress syndrome during the disease. Also, those who took vitamin D recorded an increase in the formation of IgG to the SARS-CoV-2 virus 2 months after infection 3.8 times higher than the values recorded in respondents who did not take cholecalciferol. The participants who took cholecalciferol suffered the infection more severely, especially if they used any other protective substances. Also, with the preventive intake of vitamin D after COVID-19, increased fatigue persisted longer, the appearance of new and activation of chronic diseases and muscle, joint and vertebral pains that appeared for the first time were reported more often, which correlates with the data we received earlier.

Keywords: COVID-19, cholecalciferol, riamilovir, umifenovir hydrochloride monohydrate, ascorbic acid, zinc, IFNα-2b human recombinant, joint, spine

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Introduction

The current direction of scientific research in recent years has been the study of the immunobiological properties of vitamins, in particular substances belonging to group D [12]. It is no secret that the surge of such interest is associated with the appearance of commercially available test systems on the market. Great hopes were pinned on the use of vitamin D as a means of reducing the spread of the 2019 pandemic. The assumptions were based on the established facts of the involvement of 25(OH)D in the regulatory [7] and protective [1] reactions in a new coronavirus infection. Previously, it was reported that cholecalciferol may have some protective properties in relation to reducing the risk of infection with the SARS-CoV-2 virus, the severity of the infectious process [10], as well as mortality from COVID-19 [5].

Data were presented on the important role of vitamin D in the prevention of the persistence of the pathogen in the human population [13]. A local study aimed at studying the feasibility of using cholecalciferol for the prevention of a new coronavirus infection, regardless of the use of specific immunotropic drugs, in particular vaccines, remains relevant. The purpose of this work was to analyze the results of oral administration of cholecalciferol in order to prevent infection with the SARS-CoV-2 virus in the first wave of the COVID-19 pandemic.

Materials and methods

The study was performed in the period from October 07 to December 29, 2020 (in the first wave of a new coronavirus infection) at the time of the absence of immunobiological drugs developed and approved for clinical use for specific prevention of COVID-19. There were no registered vaccines at the time of the study. This made it possible to evaluate the protective properties of vitamin D in infection caused by the SARS-CoV-2 virus.

The study of the data was based on the fulfillment of two mandatory conditions for respondents. The first condition was: the presence of direct contact with a primarily untreated contingent of patients, among whom there could potentially be and were cases of a new coronavirus infection. The second condition was: compliance with generally accepted preventive measures, primarily barrier measures, to prevent infection with the SARS-CoV-2 virus, namely: the use

of personal protective equipment (disposable medical masks), hand sanitizing liquids / wearing disposable gloves and distancing, such as could be possible in the conditions of performing their work functions.

All study participants personally filled out questionnaires to assess the nature and severity of the course of a new coronavirus infection, premorbid and postmorbid status, and also gave written voluntary informed consent to the use of the information obtained, including medical information. The above gave grounds to assert that the rights of patients specified in the provisions of the Order of the Ministry of Health of the Russian Federation No. 266 of 19.06.2003 "On approval of the Rules of Clinical Practice in the Russian Federation", international documents based on the "Helsinki Declaration of the World Medical Association" and its subsequent editions, documents of the United Nations, were not violated. The life and health of the participants of the clinical and laboratory study were not in danger. Before the analytical work, all open personal data was anonymized. The study and analysis of the collected information was carried out with the approval of the local ethical committee of the medical organization.

All the study participants were employees of a multidisciplinary medical institution that provided round-the-clock emergency care to children in Ekaterinburg. The total number of respondents was 73 people. At the time of receiving the data, all participants had suffered a new coronavirus infection once. This fact was attested in the medical documentation. The causative agent of the disease is the SARS-CoV-2 virus. The diagnosis of a new coronavirus infection has been confirmed by clinical and laboratory studies. The etiological diagnosis of the disease included molecular genetic testing of samples of two localizations obtained by the conventional method (nasopharynx, oropharynx) in accordance with the provisions of the temporary methodological recommendations of the Ministry of Health of the Russian Federation. Ribonucleic acid of the SARS-CoV-2 virus was detected in all cases of infection. The concentration of antibodies to the virus was determined on average 2 months after the disease using a set of reagents SARS-CoV-2-IgG quantitative-ELISA-Best (D-5505, RU No. RZN 2021/14458, JSC Vector-Best, Russia). An approximate assessment of the concentration of IgM was carried out using a set of SARS-CoV-2-IgM-IFA-Best (D-5502, RU No. RZN 2020/10389, JSC Vector-Best, Russia).

The collection of additional information about the study participants included information about the presence of previous diseases (autoimmune, allergic, infectious, cardiovascular, and others) and addictions (tobacco smoking). The changes recorded after the disease were studied: the appearance of new or exacerbation of chronic diseases. The nature of the course of COVID-19 was also investigated: changes in the state of health, syndromes, the use of medicines and others were detected. In total, more than 70 positions were studied.

Among the study participants were those who, on their own initiative (without consulting a doctor), used immunobiological drugs to prevent infection with the SARS-CoV-2 virus. The duration of measures to prevent the disease was at least three weeks. It was found that the following were used orally: riamilovir (250 mg three times a day), umifenovir hydrochloride monohydrate (100 mg twice a week), ascorbic acid (a solution of 250 mg of dry matter in 200 mL of boiled chilled water twice a day), zinc acetate (100 mg once a day [9]), cholecalciferol (625-1250 IU once a day). Human recombinant interferon alpha-2b was also administered intranasally at a dosage of 3000 ME in each nasal passage twice a day. None of the study participants had previously been vaccinated against the SARS-CoV-2 virus. The decision to use non-specific immunoprophylactic agents was made by the participants independently after the WHO announced a pandemic of coronavirus infection. Taking into account the fact that all respondents were employees of a medical institution, including doctors, nursing staff, or had access to consultations on the specifics of taking immunobiological agents, in this study we believed that the implementation of preventive measures for the use of the above substances was carried out exactly in accordance with the described schemes.

Among the total number of participants, 28 people (38.4%) took cholecalciferol in order to prevent infection with the SARS-CoV-2 virus (group No. 1) and 45 people (61.6%) did not use it (group No. 2). In group No. 1 there were 8 (28.6%) doctors, 10 (35.7%) people with secondary and 2 (7.1%) with junior medical education, as well as 8 (28.6%) people of other medical institution personnel; group No. 2 consisted of 14 (31.1%) doctors, 26 (57.8%) nurses, 1 (2.2%) junior medical officer, as well as 4 (8.9%) specialist hospital support staff. In the first group there were 2 (7.1%) men in the second – 8 (17.8%). Median and interquartile age range of group No. 1 was 54.0 (45.8-62.3) years, group No. 2 – 44.5 (32.0-49.0) years. Anthropometric data (height, weight, body mass index) had no significant differences between the groups and fluctuated within the physiological norm.

Statistical processing of the obtained data was performed using the Windows 10 operating system (Microsoft Corporation, USA): STATISTICA v.12.5.192.5 statistical package (StatSoft, Inc., USA). The data are presented in the form of the number of cases, percentage of the total number of people in the group, median (Me) and interquartile range ($Q_{0.25}$-$Q_{0.75}$). The studied indicators had mainly

a categorical type of data. The normality of the distribution was checked using the Kolmogorov–Smirnov test, where the value of $p < 0.05$ indicated an abnormal distribution of the studied data. The differences between the groups were evaluated using Chi-Square test. The significance level (p-value) of the probability of rejection of the accepted statistical hypothesis was considered equal to 0.05. To assess the differences between the two study groups, the Wald–Wolfowitz Runs Test was also used, the differentiation was based on p-level values < 0.05. The third criterion was the Kruskal–Wallis test, which was used to assess the significance of the differences between four unrelated groups. Linear Discriminant Analysis was used in the work.

The expert opinion on the possibility of open publication of the obtained data was approved by the members of the expert commission of the Institute of Immunology and Physiology of the Ural Branch of the Russian Academy of Sciences before the transfer of information to the open press.

Results and discussion

Seventy-three people were examined, of whom 28 (38.4%) took cholecalciferol in order to prevent infection with the SARS-CoV-2 virus (group No. 1) and 45 people (61.6%) did not use it (group No. 2). The first stage of the study was a frequency comparative analysis of the data obtained at different stages of observation: before infection with the virus, during the disease and after two months of observation.

It was found that patients who took vitamin D before the disease were more likely (3.1 times) to have metabolic syndrome or type 2 diabetes: 21.4% versus 6.7% in group No. 2. Also, recipients who used cholecalciferol had hypertension more often (3.2 times) before the disease (50.0% vs. 15.6% in group No. 2). At the same time, the revealed differences were not statistically significant (based on Chi-Square test and Wald–Wolfowitz Runs Test). It is assumed that on the one hand, the reason for the discovered fact could be some age difference between the groups. On the other hand, the presence of concomitant pathology in respondents could cause a desire to reduce the risk of infection with the virus. And during the announcement of the coronavirus pandemic, patients used non-specific immunoprophylactic agents.

We studied data on the presence of changes in the cardiovascular system before COVID-19 (in particular, the presence of coronary heart disease, chronic heart failure, myocardial infarction, stroke, and others), the pulmonary system (chronic obstructive disease, emphysema, and others), the immune system (autoimmune and allergic reactions), the excretory system (kidney diseases). There were no differences between the groups. Groups No. 1 and No. 2 also did not differ in the number of annual previously tolerated acute respiratory viral infections. The frequency of hemocontact infections (HIV, hepatitis B, C), the presence of addictions (smoking) were also similar in both groups. The drug therapy available before the disease (hormones, sedatives, antidepressants, etc.)

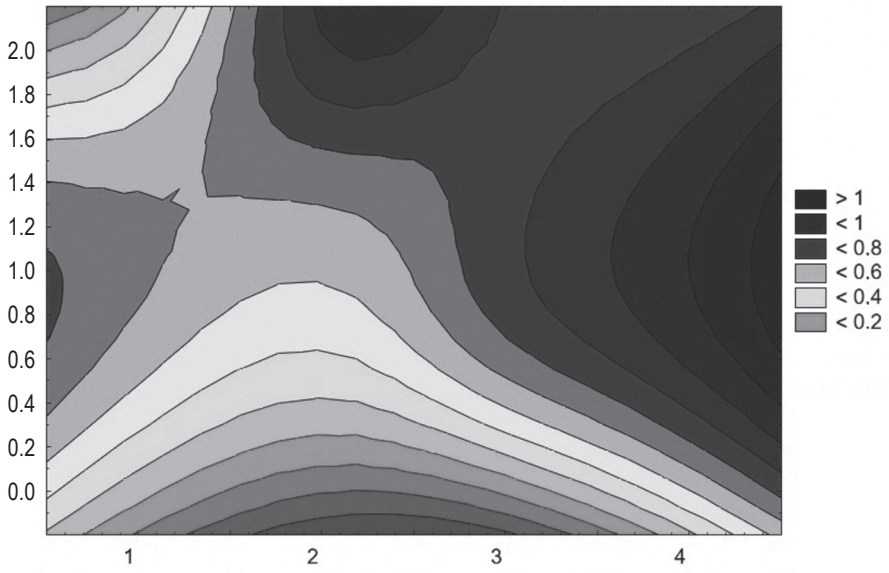

Figure 1. 3D Contour Plot of assessment of the severity of infection by study participants 2 months after the disease

Note. Horizontally, numbering of subgroups of participants: 1, did not use any immunoprophylactic agents (32 people); 2, did not take vitamin D, but took other immunoactive substances (13 people); 3, only vitamin D was taken to prevent infection (10 people); 4, vitamin D and other immunoactive substances were used (18 people); vertically, assessment of the severity of infection in points: 0, mild degree, 1, medium degree, 2, severe degree (darker color, heavier infection).

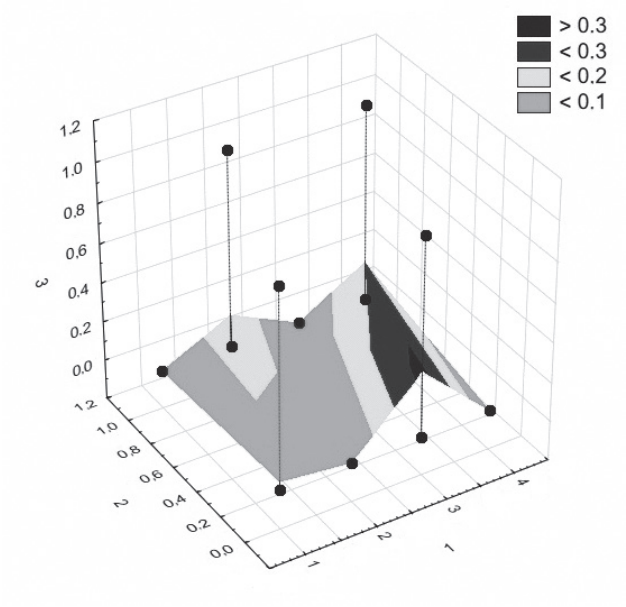

Figure 2. 3D Wafer Plot of assessment of the appearance of new diseases, as well as muscle and joint pain after Covid-19, depending on the use of immunoprophylactic agents

Note. On axis 1, numbering of subgroups of participants: 1, no immunoprophylactic agents were used; 2, did not take vitamin D, but took other immunoactive substances; 3, only vitamin D was taken to prevent infection; 4, vitamin D and other immunoactive substances were used; on axis 2, the appearance of joint and muscle pain (in points: 1, yes; 0, no); on axis 3, the appearance of new diseases after COVID-19 (in points: 1, yes; 0, no).

was the same. In general, the premorbid status of respondents in both groups was similar.

Analyzing the data on changes during COVID-19, it was found that the frequency of feverish conditions and the development of pneumonia in groups No. 1 and No. 2 was the same. None of the study participants were in the intensive care unit or on artificial ventilation. The median hospitalization time for groups No. 1 and No. 2 was 4 (0-11) and 0 (0-10) days, the duration of treatment was 21 (16-30) and 21 (14-28) days, respectively. Prophylactic administration of cholecalciferol had no effect on the development of pulmonary insufficiency and on the volume of lung tissue damage. The destruction was assessed by studying the results of computed tomography. Also, during the illness, there were no significant differences between the groups in the frequency of occurrence of neurological disorders, anosmia, dysgeusia and DIC syndrome. At the same time, there were differences in the frequency of development of respiratory distress syndrome. In particular, in patients taking cholecalciferol, the syndrome did not develop at all, in group No. 2 it was registered in 20.0% of cases (Chi-Square = 5.242, p = 0.02).

In this study, clinical and laboratory data after COVID-19 were evaluated. It was found that in patients of group No. 1, the concentration of IgG after 2 months was 3.8 times higher than the values in group No. 2 (Chi-Square = 9.268, p = 0.003) and amounted to 18.8 (18.0-21.7) BAU/mL (binding antibody units), whereas in patients who did not take vitamin D, IgG level was 5.0 (4.8-5.6) BAU/mL. The use of Linear Discriminant Analysis (Discriminant Function Analysis) allowed us to establish that in addition to the concentration of IgG in patients of the two groups, the level of class M immunoglobulins had statistically significant differences (Wilks' Lambda: 0.659 approx. F (7.32) = 2.367 p < 0.045) – after taking cholecalciferol, it was higher.

If we recall, in both groups (No. 1 and No. 2) there were respondents who used other immunoactive substances for preventive purposes, such as: riamilovir, umifenovir hydrochloride monohydrate, human recombinant interferon alpha-2b, zinc acetate, vitamin C. In the first group there were 18 such people (24.7% of all participants, 64.3% of those who took cholecalciferol). In the second group, there were 13 such respondents (17.8% of all participants, 28.9% of those who did not take cholecalciferol). Analysis of the data obtained using the Kruskal–Wallis test for four unrelated groups in assessing the differences in the severity of the infection showed the following. A graphical explanation of the data obtained is presented in Figure 1.

It was found that those who used other immunoactive substances and did not take vitamin D suffered the disease more easily than everyone else. The next in severity of infection were respondents who did not use any immunoprophylactic agents. Respondents who took cholecalciferol mainly assessed the severity of infection as average. The study participants who took both vitamin D and used other means of prevention suffered the most from COVID-19. An additional pairwise comparison of the data obtained showed that there were significant differences between those who did nothing and those who selectively took vitamin D (Chi-Square = 4.421, p = 0.004).

In this study, additional information was obtained that respondents who took cholecalciferol were more likely than others to report long-term fatigue (at least up to two months after the disease), as well as exacerbation of chronic and the appearance of new diseases (hypertension, cardialgia, bronchial asthma, allergies, decreased visual acuity), first-time muscle, joint and vertebral pains (Figure 2).

The phenomenon of arthralgia and other lesions of large joints in COVID-19 has already been described by us earlier [4]. Studies by other authors also report frequent complaints of increased fatigue, joint pain and myalgia, in general, musculoskeletal symptoms of

COVID-19 [6, 8]. At the same time, the role of vitamin D is considered exclusively from the standpoint of its insufficiency in a new coronavirus infection and its potential role in inhibiting hyperinflammatory reactions, as well as accelerating the healing process of affected areas, especially in lung tissue [2, 3].

Currently, the post-acute sequelae of COVID-19 is widely studied [11], which can manifest itself by the activation of chronic diseases and the appearance of new diseases due to infection [14]. As part of this, new information about the course of the distant period of COVID-19 is expected to appear in the near future. Also in this regard, do not forget that the effect of vitamin D can be not only phenotypic, but also determined by the polymorism of genes that regulate the transport and metabolism of the compound. The differences may also be related to insolation and other factors that deserve additional study [15].

Conclusion

In this study, the results of daily oral administration of cholecalciferol at a dose of 625-1250 IU were evaluated in order to prevent infection with the SARS-CoV-2 virus. It was found that vitamin D intake did not affect the incidence of fever, the incidence of lung pneumonia, as well as the volume of lung tissue damage (based on computed tomography data), the duration of hospitalization and the disease as a whole, and also did not prevent the development of anosmia and dysgeusia.

The use of vitamin D as a protective agent to prevent infection with the SARS-CoV-2 virus has had an impact on reducing the frequency / prevention of cases of respiratory distress syndrome during the disease. In particular, not a single case of this syndrome was detected in those taking cholecalciferol, whereas in the rest the syndrome was detected in 20% of cases. Also, those taking vitamin D recorded an increase in the formation of IgG to the SARS-CoV-2 virus 2 months after infection 3.8 times higher than the values recorded in respondents who did not take cholecalciferol.

Participants who took cholecalciferol suffered the infection more severely, especially if they used any other protective substances. Also, with the preventive intake of vitamin D after COVID-19, increased fatigue persisted longer, the appearance of new and activation of chronic diseases and muscle, joint and vertebral pains that appeared for the first time were reported more often, which corresponds to our data obtained earlier.

The limitation of the information obtained in this study may be a small sample of the study and, perhaps, as we now believe, a low dose of vitamin D taken, which was due to the lack of recommendations on the amount of vitamin intake at the time of the announcement of the COVID-19 pandemic.

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