INTERNAL DISEASES

INFLUENCE OF HEALTH RESORT TREATMENT ON THE LEVEL OF SYSTEMIC INFLAMMATION IN PATIENTS AFTER NEW CORONAVIRUS INFECTION

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ABSTRACT

Background. *Low-grade inflammation is currently one of the main risk factors for the development of adverse events in the cardiovascular system, including death from cardiovascular diseases or their complications that cause mortality in the post-COVID period.*

The aim of the study. *To assess the impact of health resort treatment in the conditions of the Southern Coast of Crimea on clinical and functional parameters, as well as on the level of systemic inflammation in patients after a new coronavirus infection.*

Materials and methods. *The study included 67 patients (54.9 ± 9.05 years) in the post-COVID period who underwent health resort treatment at the I.M. Sechenov Academic Research Institute of Physical Treatment Methods, Medical Climatology and Rehabilitation. Methods of health resort treatment included climatic treatment on the Southern Coast of Crimea, therapeutic breathing exercises, terrainkur, and various methods of respiratory therapy. In all patients, the study of the C-reactive protein (CRP) in peripheral blood upon admission and at discharge was carried out.*

Results. *Despite a statistically significant improvement in most clinical and functional parameters, the level of CRP and the number of leukocytes and their subpopulations in peripheral blood in patients who underwent health resort treatment did not differ significantly ($p > 0.05$) from the baseline values obtained upon admission at the I.M. Sechenov Academic Research Institute of Physical Treatment Methods, Medical Climatology and Rehabilitation. The CRP index upon admission and at discharge corresponded to the lower limit of the interval specific for low-grade inflammation (from 3 to 10 mg/l).*

Conclusion. *Our results indicate the lack of effectiveness of the presented plan of health resort treatment in the correction of low-intensity inflammation, as well as the necessity for deeper scientific research in the direction of studying the mechanisms of low-grade inflammation development and the methods of its management.*

Key words: *SARS-CoV-2, inflammation, health resort treatment, post-COVID, CRP*

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ВЛИЯНИЕ САНАТОРНО-КУРОРТНОГО ЛЕЧЕНИЯ НА УРОВЕНЬ СИСТЕМНОГО ВОСПАЛЕНИЯ У ПАЦИЕНТОВ, ПЕРЕНЁСШИХ НОВУЮ КОРОНАВИРУСНУЮ ИНФЕКЦИЮ

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РЕЗЮМЕ

Обоснование. *Низкоинтенсивное воспаление (НИВ) на данный момент является одним из главных факторов риска развития неблагоприятных событий со стороны сердечно-сосудистой системы, включая смерть от сердечно-сосудистых заболеваний или их осложнений, обуславливающих смертность в постковидном периоде.*

Цель исследования. *Оценить влияние санаторно-курортного лечения в условиях Южного берега Крыма на клинические и функциональные показатели, а также на уровень системного воспаления у пациентов, перенёсших новую коронавирусную инфекцию.*

Материалы и методы. *Обследовано 67 пациентов (возраст – 54,9 ± 9,05 года) в постковидном периоде, проходивших санаторно-курортное лечение в ГБУЗ РК «Академический научно-исследовательский институт физических методов лечения, медицинской климатологии и реабилитации имени И.М. Сеченова». Методы санаторно-курортного лечения включали климатотерапию на Южном берегу Крыма, лечебную дыхательную гимнастику, терренкуры, различные методы респираторной терапии. Всем пациентам было проведено исследование уровня С-реактивного белка (СРБ) в периферической крови при поступлении и на момент выписки.*

Результаты. *Несмотря на статистически значимое улучшение большинства клинических и функциональных показателей, уровень СРБ и количество лейкоцитов и их субпопуляций в периферической крови у пациентов, прошедших санаторно-курортное лечение, статистически значимо не отличались ($p > 0,05$) от исходных показателей, полученных в день поступления в ГБУЗ РК «Академический научно-исследовательский институт физических методов лечения, медицинской климатологии и реабилитации имени И.М. Сеченова». Показатель СРБ при поступлении и выписке соответствовал нижней границе интервала, характерного для НИВ (от 3 до 10 мг/л).*

Заключение. *Полученные нами результаты свидетельствуют о отсутствии эффективности представленного плана санаторно-курортного лечения в коррекции НИВ, а также о необходимости более глубоких научных изысканий в направлении изучения механизмов формирования НИВ и методов борьбы с данным состоянием.*

Ключевые слова: *SARS-CoV-2, воспаление, санаторно-курортное лечение, постковид, СРБ*

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The manifestations of the new coronavirus infection (NCI) acute period are only the tip of the iceberg that modern public health is already facing. The number of people with SARS-CoV-2 as of January 20, 2023 is estimated to be more than 500 million, and this number is increasing every day [1]. The diversity and unpredictability of distant manifestations of NCI makes the post-COVID period an extremely dangerous interval of time. Complications from various organs and systems can lead to both disability and fatal outcome due to the development of life-threatening conditions [2].

Despite the polymorphic manifestations of post-COVID syndrome, systemic inflammation and disturbance of the hemostasis system are undoubtedly an important part of all disorders [2]. The role of low-grade systemic inflammation is often completely underestimated.

The main indicator characterizing the status of low-grade inflammation (LGI) is the level of C-reactive protein (CRP) in peripheral blood ranging from 3 to 10 mg/L [3, 4]. Currently, LGI status is a risk factor for cardiovascular adverse events (including death from cardiovascular disease (CVD) or complications) [5]. Cardiovascular events are one of the most common manifestations of post-COVID syndrome, accounting for post-COVID mortality [6].

In connection with the above, it is of utmost importance to search for the most effective methods of combating low-grade inflammation at the stage of health resort treatment of the post-COVID patient.

The aim of our study was to evaluate the effect of health resort treatment in the conditions of the Southern coast of Crimea on clinical and functional parameters, as well as the level of systemic inflammation in patients who had a new coronavirus infection.

MATERIALS AND METHODS

The study included 67 patients admitted to the Pulmonology Department of the I.M. Sechenov Academic Research Institute of Physical Treatment Methods, Medical Climatology and Rehabilitation for health resort treatment after a new coronavirus infection.

Women accounted for 58.2 % ($n = 39$) of the study population, men – 41.7 % ($n = 28$); mean age – 54.9 ± 9.05 years.

An average of 160 ± 18 days passed from the onset of the first symptoms to the patient's admission to the Pulmonology Department.

The inclusion criteria for the study were: new coronavirus infection and referral to health resort treatment within more than 14 days after discharge from the Infectious Disease Hospital or recovery, as well as the absence of concomitant pathologies.

Exclusion criteria were: presence of complicated forms of previous viral pneumonias with expressed functional pulmonary and extrapulmonary disorders; age more than 75 years; general contraindications for health resort treatment. Patients were included in the study after signing informed consent.

All patients on admission were clinically examined and medical history data were collected. On admission and at discharge, the patients underwent laboratory examination of peripheral blood, and clinical and functional parameters were assessed. Interpretation of clinical symptoms (cough and dyspnea) was performed using a three-point scale, according to which 1 point – moderate severity; 2 points – medium severity; 3 points – pronounced clinical symptom. Function tests included electrocardiogram, spirogram with determination of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and inspiratory capacity (IC). The mMRC (Modified Medical Research Council) Dyspnea Scale, OCD (Oxygen Cost Diagram) and VAS (Visual Analogue Scale) were used.

Methods of health resort treatment: nebulizer therapy with bronchodilators and mucolytics as needed; halo-inhalation therapy using Galoneb apparatus; exercises on Coach 2 breathing simulators with inspiratory load; high frequency chest wall oscillation; diaphragmatic breathing training; hypercapnic-hypoxic training; chest massage; therapeutic exercises (breathing assembly); physiotherapy methods (magnetic therapy on the chest); Terrainkur; climatotherapy (round-the-clock or dosed aerotherapy); air and sun baths; sea bathing.

Data were analyzed using licensed Statistica 12 statistical software (StatSoft Inc., USA). Initially, all studied indicators were tested for normality of distribution using the Shapiro-Wilk W-test; samples in which the test was $p \geq 0.1$ were taken as normal distribution, while the W test value of $p < 0.1$ was taken as non-normal distribution. When processing non-parametric data, the Wilcoxon T-test for related samples was used to compare groups. Indicators were considered statistically significant at $p < 0.05$. Under normal distribution, the paired Student's T-test for related samples was used to handle non-parametric data to compare groups. Indicators were considered statistically significant at $p < 0.05$.

RESULTS

As can be seen from the data presented in Table 1, patients who had a new coronavirus infection and underwent health resort treatment showed a statistically significant decrease in the frequency and severity of cough, severity of dyspnea, feeling of heaviness in the chest and fatigue ($p < 0.001$). A statistically significant increase in distance in the 6-minute walk test ($p < 0.001$), a decrease in the mMRC Dyspnea Scale and a positive trend in OCD ($p < 0.001$) and VAS ($p < 0.05$) were recorded. There was also a statistically significant improvement in FVC and IC ($p < 0.05$).

Despite the statistically significant improvement of most clinical and functional parameters, the level of CRP and the number of leukocytes and their subpopulations in the peripheral blood of patients who underwent health resort treatment, statistically significantly did not differ ($p > 0.05$) from the baseline values obtained on the day of admission to the I.M. Sechenov Academic Research Institute of Physical Treatment Methods, Medical Climatology and Rehabilitation. The CRP index upon admission and at discharge corresponded to the lower limit of the in-

TABLE 1

CLINICAL AND FUNCTIONAL PARAMETERS, M ± σ

Parameters	Before treatment	After treatment	Statistical significance of differences, *p*
Cough – frequency, points	0.731 ± 0.962	0.257 ± 0.532	$p < 0.001$
Cough – severity, points	0.492 ± 0.704	0.208 ± 0.409	$p < 0.001$
Dyspnea – severity, points	1.208 ± 0.879	0.507 ± 0.587	$p < 0.001$
Feeling of heaviness in the chest, points	0.477 ± 0.704	0.044 ± 0.208	$p < 0.001$
Fatigue, score	1.059 ± 0.850	0.268 ± 0.479	$p < 0.001$
Diastolic BP, mm Hg	79.720 ± 0.842	79.121 ± 0.566	$p > 0.05$
FVC, %	102.402 ± 2.188	105.310 ± 2.339	$p < 0.05$
FEV1, %	97.372 ± 2.425	98.212 ± 2.182	$p > 0.1$
IC, %	96.536 ± 3.879	102.356 ± 3.115	$p < 0.05$
6-Minute Walk Test, m	502.742 ± 10.883	532.136 ± 8.847	$p < 0.001$
mMRC Dyspnea Scale, points	1.380 ± 0.084	1.174 ± 0.090	$p < 0.05$
Oxygen Price Chart, points	6.891 ± 0.208	7.835 ± 0.300	$p < 0.001$

Note. The table shows the quantitative (M ± σ) attributes. Statistical significance of differences between the values of indicators before and after health resort treatment was calculated using Student's T-test for related samples. BP - blood pressure.

terval specific for low-grade inflammation (3 to 10 mg/L) (Table 2). The values of the main biochemical markers were also not statistically significantly different ($p > 0.05$) from the baseline values obtained on the day of admission.

DISCUSSION

In contrast to acute inflammation caused by injury or acute infection and accompanied by marked dysfunction and symptoms and signs from organs and organ systems, chronic low-grade systemic inflammation may go undetected for years and be detected only by routine laboratory tests. However, despite the paucity of symptoms, gradually disrupting metabolic and repair processes in intact tissues, chronic inflammation leads to the development of numerous age-related diseases, functional and morphological reorganization of organs and organ systems and increased risk of life-threatening conditions [7].

The role of inflammation in the pathophysiology of the early stages of diseases associated with atherothrombotic complications has been recognized for more than 25 years. A number of inflammatory mediators produced by leukocytes attracted to the damaged subendothelial compartment of arteries contribute to the progression of atherosclerosis. This effect is multifactorial and is determined by the increased migration of new leukocytes into the lesion area, promoting the formation of altered macrophages – foam cells containing lipids [8], increased expression of endothelial adhesion molecules [9] and stimulation of smooth muscle cell proliferation [10], which ultimately causes plaque instability [11] and rupture [12, 13].

In addition, inflammation is an important determinant of the onset and development of dysmetabolic disorders, increasing the risk of type 2 diabetes mellitus, non-alcoholic fatty liver disease (NAFLD), and CVD [14].

The state of LGI itself is a polyethiologic problem. The current literature explains the occurrence of LGI, on the one hand, by uncorrectable genetic traits of an individual, namely, the presence of single-nucleotide polymorphisms of genes of the main proinflammatory molecules [15], and, on the other hand, by conditions that are amenable to therapeutic intervention, such as increased intestinal permeability to certain bacterial proinflammatory com-

TABLE 2

LABORATORY INDICATORS, ME [Q1; Q3]

Indicators	Before treatment	After treatment	Statistical significance of differences, *p*
Cholesterol, mmol/L	5.7 [5.0; 6.8]	5.8 [4.8; 6.5]	$p > 0.05$
Glucose, mmol/L	5.4 [4.8; 6.0]	5.2 [4.9; 5.7]	$p > 0.05$
ALT, u/l	22.5 [19.0; 28.6]	22.2 [17.1; 27.2]	$p > 0.05$
AST, u/l	25.05 [21.7; 30.9]	24.6 [19.8; 29.7]	$p > 0.05$
LDH, u/l	311.0 [263.0; 351.0]	329.0 [297.0; 379.0]	$p > 0.05$
ALP, u/l	142.0 [110.0; 165.0]	149.0 [113.0; 182.5]	$p > 0.05$
Creatinine, μmol/l	88.5 [81.5; 96.0]	87.0 [79.0; 97.0]	$p > 0.05$
Urea, mmol/l	5.1 [4.4; 6.0]	5.0 [4.2; 5.9]	$p > 0.05$
Total protein, g/l	78.0 [72.0; 80.0]	77.0 [71.5; 80.0]	$p > 0.05$
Albumin, g/l	37.0 [36.0; 39.0]	39.0 [36.0; 40.0]	$p > 0.05$
CRP, mg/l	3.0 [3.0; 4.0]	3.0 [3.0; 4.0]	$p > 0.05$
Absolute Leukocyte Count, 10^9/l	6.0 [5.1; 7.4]	6.2 [5.3; 7.5]	$p > 0.05$
Absolute Neutrophil Count, 10^9/l	3.5 [2.7; 4.5]	3.4 [2,6; 4.3]	$p > 0.05$
Absolute Lymphocyte Count, 10^9/l	1.8 [1.5; 2.2]	1.8 [1.4; 2.3]	$p > 0.05$
Absolute Monocyte Count, 10^9/l	0.4 [0.2; 0.5]	0.4 [0.2; 0.6]	$p > 0.05$
Absolute Band Neutrophil Count, 10^9/l	0.2 [0.1; 0.3]	0.1 [0.1; 0.3]	$p > 0.05$
Absolute Segmented Neutrophils Count, 10^9/l	3.2 [2.5; 4.1]	3.2 [2.5; 4.0]	$p > 0.05$

Note. The table presents quantitative (Me [Q1; Q3]) attributes. Differences in quantitative attributes were identified using the Wilcoxon test. ALT — alanine aminotransferase; AST – aspartate aminotransferase; LDH – lactate dehydrogenase; ALP – alkaline phosphatase.

ponents [16] and the presence of chronic infection [17], on the other hand, conditions that are amenable to therapeutic intervention, such as increased intestinal permeability to certain bacterial proinflammatory components [16], the presence of chronic infection [17], and dysmetabolic disorders, in particular obesity and type 2 diabetes mellitus [18].

Low-grade inflammation certainly aggravates the course of the acute period of SARS-CoV-2 infection, and in this case, the already existing chronic dysregulation of the immune system is complicated by the accession of acute infection, which is rather complicated in pathogenetic terms [19]. This combination of chronic and acute processes leads to certain consequences on the part of organs and systems and in the post-COVID period, primarily changing the homeostasis of the cardiovascular system and hemocoagulation system, increasing the risk of fatal complications [5, 6].

In this regard, the control of LGI in post-COVID patients is, in our opinion, one of the highest priorities to ensure the health of the population now and in the postpandemic period. To address this problem, it is necessary to eval-

uate the impact of already available and applied methods of health resort treatment used in the post-COVID period and, if necessary, to make adjustments to existing protocols for the management of post-COVID patients.

In our study, the patients underwent health resort treatment in the conditions of the Southern Coast of Crimea, received therapeutic diets, therapeutic breathing exercises and various methods of respiratory therapy.

Despite the significant clinical effect and improvement of functional parameters, the main marker of systemic inflammation in these patients did not undergo statistically significant changes and remained at the level corresponding to the lower limit of the interval specific for LGI (from 3 to 10 mg/l) (Table 2).

A number of other biochemical indicators also did not change statistically significantly, but most of the indicators were within the reference range (Table 2).

The mechanism of anti-inflammatory effect of exercise affecting the ratio of proinflammatory and anti-inflammatory cytokines has been described in the literature [20, 21]; however, in our study, a course of therapeutic exercise (24 days) had no significant effect on LGI status in post-COVID patients.

Based on the possible causes of LGI listed above, such methods can be pharmacological and non-pharmacological interventions aimed at regulating the permeability of the intestinal barrier, improving the liver, sanitation of chronic foci of infection and correction of dysmetabolic processes.

CONCLUSIONS

Complex health resort treatment of patients in the post-COVID period is accompanied by improvement of clinical and functional parameters and general condition. Health resort treatment has practically no significant effect on the change of the main laboratory biochemical indicators. Currently available methods of health resort treatment do not affect the level of low-grade systemic inflammation in patients in the post-COVID period. All this determines the need for more profound scientific research to study the mechanisms of LGI formation and methods of combating this condition.

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Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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