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PARAMETERS OF THE LIPID PROFILE IN DONORS WHO HAD SUFFERED FROM COVID-19 AND HAD VARIOUS TITERS OF ANTI-SARS-CoV-2 IgG IN BLOOD PLASMA

COVID-19, caused by SARS-CoV-2, is a systemic disorder of with possible pathological complications in human organism. One of the critical targets of SARS-CoV-2 is the metabolism of lipids and products, which may influence the changes in patients with illness. Currently, the mechanism of binding between SARS-CoV-2 and lipids, as well as the consequences of these processes, is unknown. In addition, the long post-COVID-19 period has been confirmed in the majority of people who have suffered from COVID-19; therefore, additional attention should be paid to studying the biochemical parameters of lipid metabolism after SARS-CoV-2 infection. Our work is aimed the studying of lipid profile including concentration of total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and triglycerides (TG) in donor groups who had suffered from COVID-19 and had different titers of anti-SARS-CoV-2 IgG in blood plasma. We selected donor groups with maximum and minimum changes of parameters among donor groups with titers of anti-SARS-CoV-2 IgG ≥ 10 Index (S/C), than we compared these groups to donor group with titer of anti-SARS-CoV-2 IgG 0 Index (S/C). We established that the donor group with titer of anti-SARS-CoV-2 95 ± 5 Index (S/C) was characterized by the maximum concentration of total cholesterol, LDL, VLDL, TG, while the donor group with titer of anti-SARS-CoV-2 75 ± 5 Index (S/C) was determined as the minimum concentration of total cholesterol, HDL, LDL. In addition, donor group with titer of anti-SARS-CoV-2 IgG 85 ± 5 Index (S/C) was described a lower concentration of VLDL and TG then in donors – 0 Index (S/C). These changes may be linked to a potential risk of cardiovascular disease (CVD). Our work can be useful for future research targeting the study of the changes in lipid metabolism during SARS-CoV-2 infection and in the development of the treatment of COVID-19 or laboratory diagnostics of physiological processes in the post-COVID-19 period.

Keywords: anti-SARS-CoV-2 IgG, total cholesterol, HDL, LDL, VLDL, TG.

Introduction. SARS-CoV-2 is the causative agent of COVID-19 disease, which caused a pandemic at the end of 2019. COVID-19 is asymptomatic or mild phase in the majority of patients, but SARS-CoV-2 infection is a risk factor for mortality in patients because it can lead to acute respiratory complications and artificial respiratory support, and fatal consequences in some cases. Frequently, patients suffering from COVID-19 have not only symptoms of respiratory system dysfunction, and the development of concomitant diseases; therefore, SARS-CoV-2 can cause systemic diseases in the body.

Clinical data have demonstrated that patients with various infections caused by gram-positive/gram-negative bacteria, viruses and parasites are characterized by changes in their lipid profile in the blood [1, 2]. In particular, a decrease in the concentrations of total cholesterol, HDL and LDL may be observed, while the concentration of TG may increase in patients. Generally, deviations from the normal range of the parameters of lipid profile correlate with the severity of the main disease; the more difficult the phase of an infection disorder, the stronger the changes in the concentrations of lipids and lipoproteins in the blood [3, 4]. Research has described [5] that patients with COVID-19 have decreased levels of total cholesterol, HDL, LDL and apolipoproteins A-1 and B, similar to other infections. Moreover, it has been reported that hypolipidemia occurs even in patients in the light phase of COVID-19 and worsens with disease progression and severity [6].

During COVID-19 the mechanism of lipid metabolism defects is currently unknown, but there are discoveries regarding the participation of lipids in viral pathogenesis [7]. Literature reports on the role of lipids in the composition of not only the viral membrane, but also the replication and invasion of the virus. Lipids that participate in the fusion of membranes and replication during penetration and exit from the membranes of host cells usually belong to the viral and human components of the cell. Significant changes in host lipidomes have been observed in cases of the difficult phase

of SARS-CoV-2 viral infection, resulting in immune system dysfunction and an increase in viral replication that can develop in the body [8]. HDL can participate in the modulation of the immune system and reactions against infectious agents. HDL binds to and neutralizes the lipids of pathogens that excessively activate the immune system during the development of COVID-19. It has been reported that HDL suppress inflammatory mediators that inactivate T cells and macrophages. The accumulation of pro-inflammatory cytokines in COVID-19 leads to the development of systemic inflammation. HDL can suppress this inflammatory cascade by inhibiting monocyte and neutrophil activation and maintaining antioxidant function, resulting in the neutralization of oxidative lipids and other factors. This process regulates inflammatory reactions in host cells [11]. In addition, LDL may oxidize, and lipid hydroperoxides accumulate during acute inflammatory reactions. The latter is esterified in oxidized LDL to activate a cascade of intracellular signaling reactions, leading to acute inflammatory reactions [9]. Moreover, an increase in the concentration of TG and a decrease in HDL can directly influence the endothelia of patients with COVID-19, which are linked to endothelial dysfunction, activation of thrombocytes and coagulation disorders. It can lead to thrombotic and/or cardiovascular disorders. These data have been reported for patients with diabetes and COVID-19 [10].

COVID-19 is closely associated with changes in the lipid metabolism. It is necessary to carefully study the main parameters of the lipid profile during and after COVID-19 for the appropriate selection of intensive therapy and prevention of lipid metabolism complications in the body.

The aim of our study was to investigate the potential changes in parameters of lipid metabolism, such as total cholesterol, HDL, LDL, VLDL and TG, in donors with different titers of anti-SARS-CoV-2 in blood plasma.

Materials and methods. People who had suffered with COVID-19 and agreed to be donors of blood plasma for biotechnological purposes at "BIOPHARMA-PLASMA" (Kyiv,

Ukraine). At the time of blood sampling, all participants were healthy. Blood plasma was collected from donors to 3-6 months after recovery from COVID-19. Donors were checked by screening tests before blood plasma was used to produce targeted biotechnological drugs. We were sent the blood plasma of donors with determined titers of anti-SARS-CoV-2 IgG for further scientific research. All donors voluntarily agreed to participate in the clinical experiment and provided written informed consent.

Anti-SARS-CoV-2 IgG titers in the blood plasma were determined by chemiluminescent microparticle immunoassay technology using the Abbott SARS-CoV-2 IgG assay (Abbott Diagnostics, Abbott Park, Illinois, United States). All donors were selected in groups based on their anti-SARS-CoV-2 IgG titers. As result, we have had such donor groups with titers of anti-SARS-CoV-2 IgG: 0 (n = 20), 10 ± 3 (n = 20); 55 ± 5 (n = 20); 65 ± 5 (n = 20); 75 ± 5 (n = 20); 85 ± 5 (n = 20); 95 ± 5 (n = 20); 125 ± 5 (n = 20); 175 ± 5 (n = 20) Index (S/C).

The concentrations of total cholesterol, HDL, LDL, VLDL, and TG were determined spectrophotometrically on a biochemical analyzer Humalyzer 3000 using standard test kits [12].

Statistical analysis of the results was performed using the computer program STATISTICA. The arithmetic mean and mean squared error indicators were calculated. The hypothesis of normal distribution was checked using the Shapiro-Wilk and Kolmogorov-Smirnov tests. All donor groups showed a non-normal distribution. So, differences between samples were determined using the Kruskal-Wallis test.

We estimated statistically significant changes in the analyzed parameters between the donor groups,

depending on the titers of anti-SARS-CoV-2 IgG. We selected the minimum and maximum changes of diagnostic parameters among the donor groups with titers of anti-SARS-CoV-2 IgG ≥ 10 ± 3 Index (S/C). The donor group with titer of anti-SARS-CoV-2 IgG 0 Index (S/C) was chosen as the reference point.

Results and discussion. The estimation of lipid metabolism demonstrated that the maximum concentrations of LDL, VLDL, total cholesterol and TG were in the donor group with titer of anti-SARS-CoV-2 IgG 95 ± 5 Index (S/C) among all donor groups (**Fig. 1**). Hyperlipidemia is a critical factor in the development of CVD. Oxidative stress can be a risk for the formation of oxidized LDL during COVID-19 infection. The accumulation leads to an imbalance in cholesterol transport, stimulates inflammation, tissue destruction and the dysfunction of endothelial cells in the vessels, resulting in the progression of atherosclerosis [13]. According to the obtained data, we assume that higher concentrations of LDL and VLDL in the donor group with titer of anti-SARS-CoV-2 IgG 95 ± 5 Index (S/C) are predictors of endothelial dysfunction that may lead to the development of atherosclerotic CVD in the post-COVID-19 period [14]. In addition, it is predicted that in the donor group with titer of anti-SARS-CoV-2 IgG 95 ± 5 Index (S/C) an increase in the concentration of TG can cause local inflammation and activation of complement and coagulation cascades, resulting in degradation of the functional status of endothelial tissue. It is linked to the accumulation of TG, which can be a signal for activation of the cleavage enzyme – lipoprotein lipase. Then, the NF-κB pathway is activated, resulting in high expression of proinflammatory cytokines, such as TNF-, IL-1, IL-6 and MCP-1 [15].

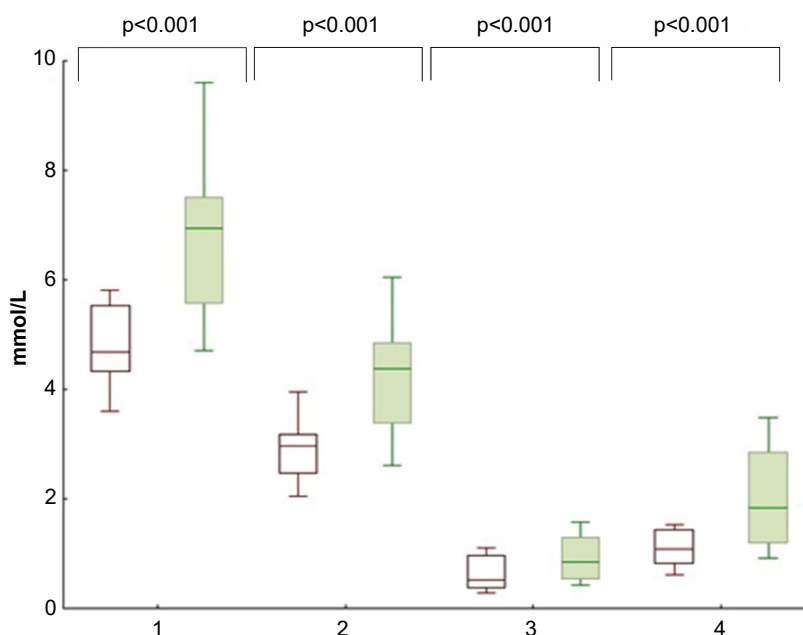


Fig. 1. The concentration of biochemical parameters of lipid metabolism:
1 – total cholesterol; 2 – LDL; 3 – VLDL; 4 – TG

□ The donor group with titer of anti-SARS-CoV-2 IgG 0 Index (S/C)
 ■ The donor group with titer of anti-SARS-CoV-2 IgG 95 ± 5 Index (S/C)

We determined that the minimum concentrations of total cholesterol, HDL and LDL were characterized for the donor group with titer of anti-SARS-CoV-2 IgG 75 ± 5 Index (S/C) among all donor groups (**Fig. 2**). It is likely that hypolipidemia in this group binds to the inflammatory

process during SARS-CoV-2 infection. Notably, the minimum concentration of HDL can be a predictor of the destruction of endothelial function and the development of vascular diseases. In the literature, changes in lipid metabolism have been linked to changes in the

dissemination of SARS-CoV-2 in organisms. Therefore, dyslipidemia in COVID-19 can be correlated with the replication of SARS-CoV-2 in cells. Changes in the energy

exchange caused by inflammatory reactions may negatively influence lipid metabolism, leading to dyslipidemia [16, 17].

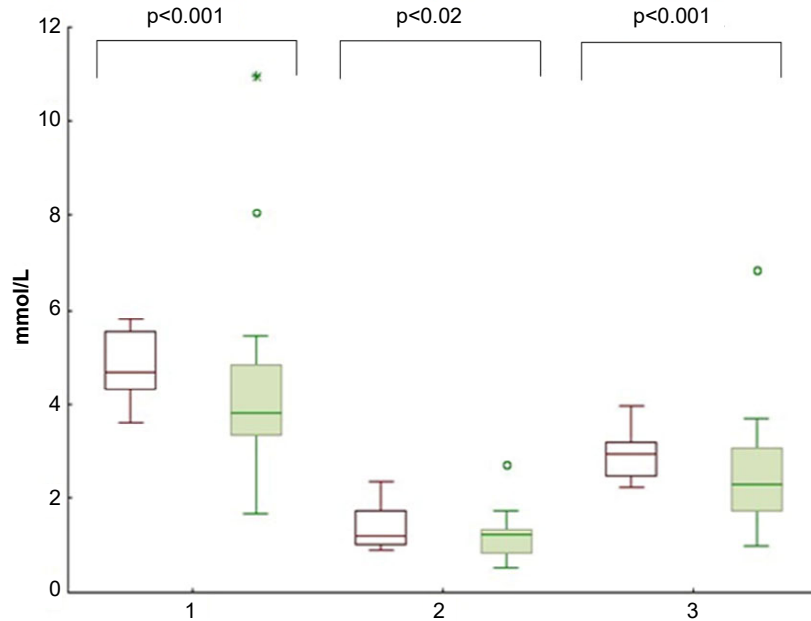


Fig. 2. The concentration of biochemical parameters of lipid metabolism: 1 – total cholesterol; 2 – HDL; 3 – LDL

□ The donor group with titer of anti-SARS-CoV-2 IgG 0 Index (S/C)
■ The donor group with titer of anti-SARS-CoV-2 IgG75 ± 5 Index (S/C)

According to the obtained lipidogram parameters, the donor group with titer of anti-SARS-CoV-2 IgG 85 ± 5 Index (S/C) was characterized by the lowest concentration of VLDL and TG among all donor groups (Fig. 3). Notably, it may be due to the decreased risk of CVD [18]. However, research has demonstrated that the concentration of these

parameters of lipid metabolism in the donor group with titer of anti-SARS-CoV-2 IgG 85 ± 5 Index (S/C) was lower than that in donors with titer – 0 Index (S/C). Because these processes can disrupt lipid metabolism, they deserve more attention in future research.

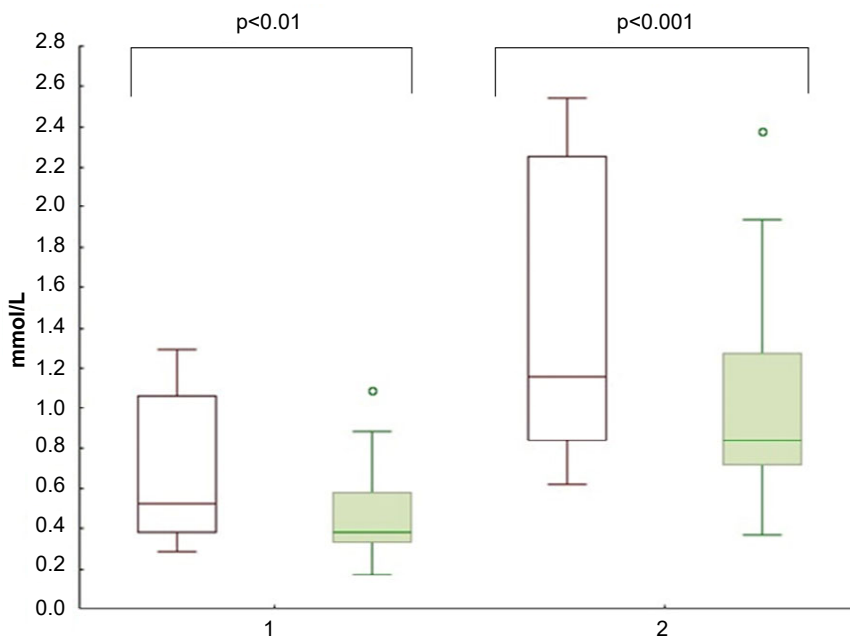


Fig. 3. The concentration of biochemical parameters of lipid metabolism: 1 – VLDL; 2 – TG

□ The donor group with titer of anti-SARS-CoV-2 IgG 0 Index (S/C)
■ The donor group with titer of anti-SARS-CoV-2 IgG85 ± 5 Index (S/C)

We discovered that the donor group with the highest concentration of HDL had titer of anti-SARS-CoV-2 IgG 10 ± 3 Index (S/C) (Fig. 4). Clinical data have shown that a decrease in HDL concentration is often observed in patients in the difficult phase of COVID-19 disease. HDL has both antioxidant and anti-inflammatory properties. Moreover, *in vitro* experiments demonstrated the antiviral

ability of HDL with regard to SARS-CoV-2 [19, 20]. We assumed that changes in HDL concentration could be a critical factor in predicting COVID-19. In addition, HDL has sufficient useful abilities; therefore, the increased concentration in the post-COVID-19 period is one of the main parameters for safety due to the negative consequences of disease for the organism.

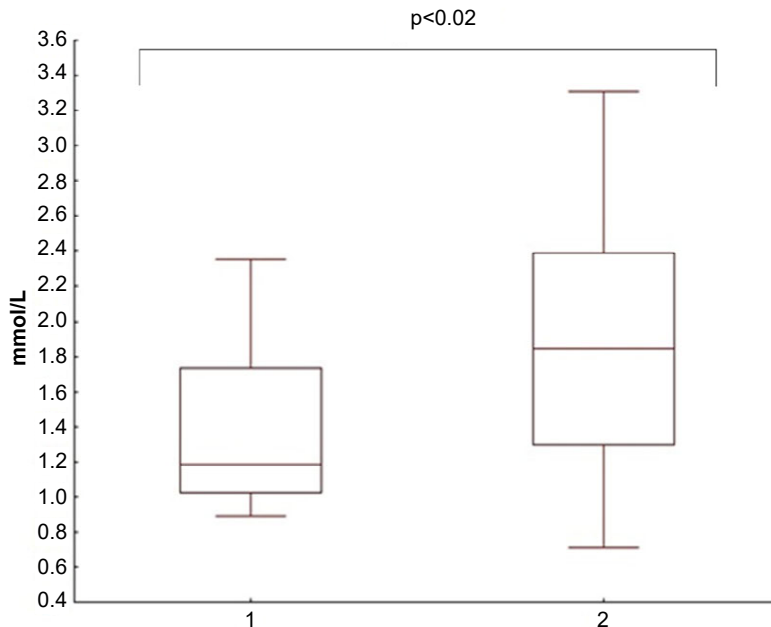


Fig. 4. The concentration of HDL in donors with titers of anti-SARS-CoV-2 IgG: 1 – 0 Index (S/C); 2 – 10 ± 3 Index (S/C)

Finally, we calculated the atherogenic index of plasma (AIP) for all donor groups. According to the results, the maximum value of AIP was obtained in the donor group with titer of anti-SARS-CoV-2 IgG 95 ± 5 Index (S/C) and the minimum – 85 ± 5 Index (S/C) (Fig. 5). These findings support previously described information. In addition, a high AIP value for the donor group with titer of anti-SARS-

CoV-2 IgG 95 ± 5 Index (S/C) and the maximum concentration of total cholesterol, LDL, VLDL and TG reported the risk of CVD development in the post-COVID-19 period. A low AIP value in the donor group with titer of anti-SARS-CoV-2 IgG 85 ± 5 Index (S/C) and minimum concentrations of VLDL and TG indicated a lower risk of CVD in the post-COVID-19 period.

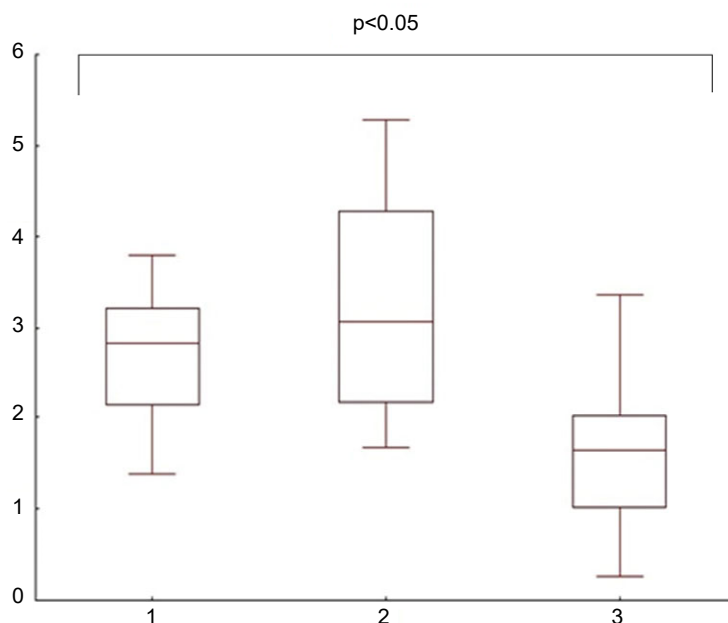


Fig. 5. The atherogenic index of plasma in donor groups with titers of anti-SARS-CoV-2 IgG: 1 – 0 Index (S/C); 2 – 95 ± 5 Index (S/C); 3 – 85 ± 5 Index (S/C)

We found that donors with titers of anti-SARS-CoV-2 IgG $\geq 10 \pm 3$ Index (S/C), including 75 ± 5 , 85 ± 5 and 95 ± 5 Index (S/C), have a potentially danger for the development of CVD. The imbalance in the lipid profile may be consequences of the inflammatory processes caused by SARS-CoV-2 and the influence of anti-SARS-CoV-2 IgG circulating in the blood.

Conclusion. In this study, we established that COVID-19 caused an imbalance in lipid metabolism, leading to hyperlipidemia, which may be a factor in the development of CVD and the spread of oxidative stress in the body, systemic inflammation, activation of complement reactions and the coagulation cascade. Our work can be useful in creating protocols for the treatment of COVID-19 and post-COVID-19 therapy to decrease the negative effects of SARS-CoV-2 and regulate lipid metabolism in organisms after recovery.

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ПАРАМЕТРИ ЛІПІДНОГО ПРОФІЛЮ У ДОНОРІВ, ЯКІ ПЕРЕХВОРИЛИ НА COVID-19 ТА МАЮТЬ РІЗНІ ТИТРИ АНТИ-SARS-CoV-2 IgG У ПЛАЗМІ КРОВІ

Захворювання COVID-19, викликане вірусом SARS-CoV-2 – це системне ураження організму з можливими патологічними наслідками для здоров'я людини. Важливими цілями для SARS-CoV-2 виступають ліпіди та продукти їхнього обміну, що впливатиме на зміни метаболізму у хворих пацієнтів. Наразі механізми взаємодії між вірусом SARS-CoV-2 і ліпідами недостатньо відомі, так само як і наслідки до яких можуть призвести такі процеси. Крім того, у більшості людей, які перенесли COVID-19, підтверджується тривалий постCOVID-19 період. Тому слід приділити додаткову увагу вивченню біохімічних показників ліпідного обміну після перенесеної інфекції SARS-CoV-2. Наша робота присвячена дослідженню ліпідного профілю, що включає концентрації загального холестерину, ліпопротеїдів високої щільності (ЛПВЩ), ліпопротеїдів низької щільності (ЛПНЩ), ліпопротеїдів дуже низької щільності (ЛПДНЩ) і тригліцеридів (ТГ) у групах донорів, які перехворіли на COVID-19 та містять у плазмі крові анти-SARS-CoV-2 IgG різних титрів. Ми відобразили групи донорів з максимальними й мінімальними змінами параметрів серед груп донорів із титрами анти-SARS-CoV-2 IgG ≥ 10 Index (S/C), потім порівняли ці групи з групою донорів із титром анти-SARS-CoV-2 IgG 0 Index (S/C). Ми встановили, що для групи донорів з титром анти-SARS-CoV-2 IgG 95 ± 5 Index (S/C) характерні максимальні концентрації загального холестерину, ЛПНЩ, ЛПДНЩ, ТГ, тоді як у групі донорів з титром анти-SARS-CoV-2 IgG 75 ± 5 Index (S/C) виявлено мінімальні концентрації загального холестерину, ЛПВЩ, ЛПНЩ. Крім цього, для групи донорів з титром анти-SARS-CoV-2 IgG 85 ± 5 Index (S/C) характерно концентрації ЛПДНЩ і ТГ нижче, ніж у контрольній групі донорів. Такі зміни можуть бути пов'язані з ризиком виникнення серцево-судинних захворювань (ССЗ). Ця робота може бути корисною у майбутніх дослідженнях, які стосуються змін метаболізму ліпідів при інфікуванні SARS-CoV-2, а також у розробці підходів лікування COVID-19 та для врегулювання процесів у постковідний період.

Ключові слова: анти-SARS-CoV-2 IgG, загальний холестерин, ЛПВЩ, ЛПНЩ, ЛПДНЩ, ТГ.