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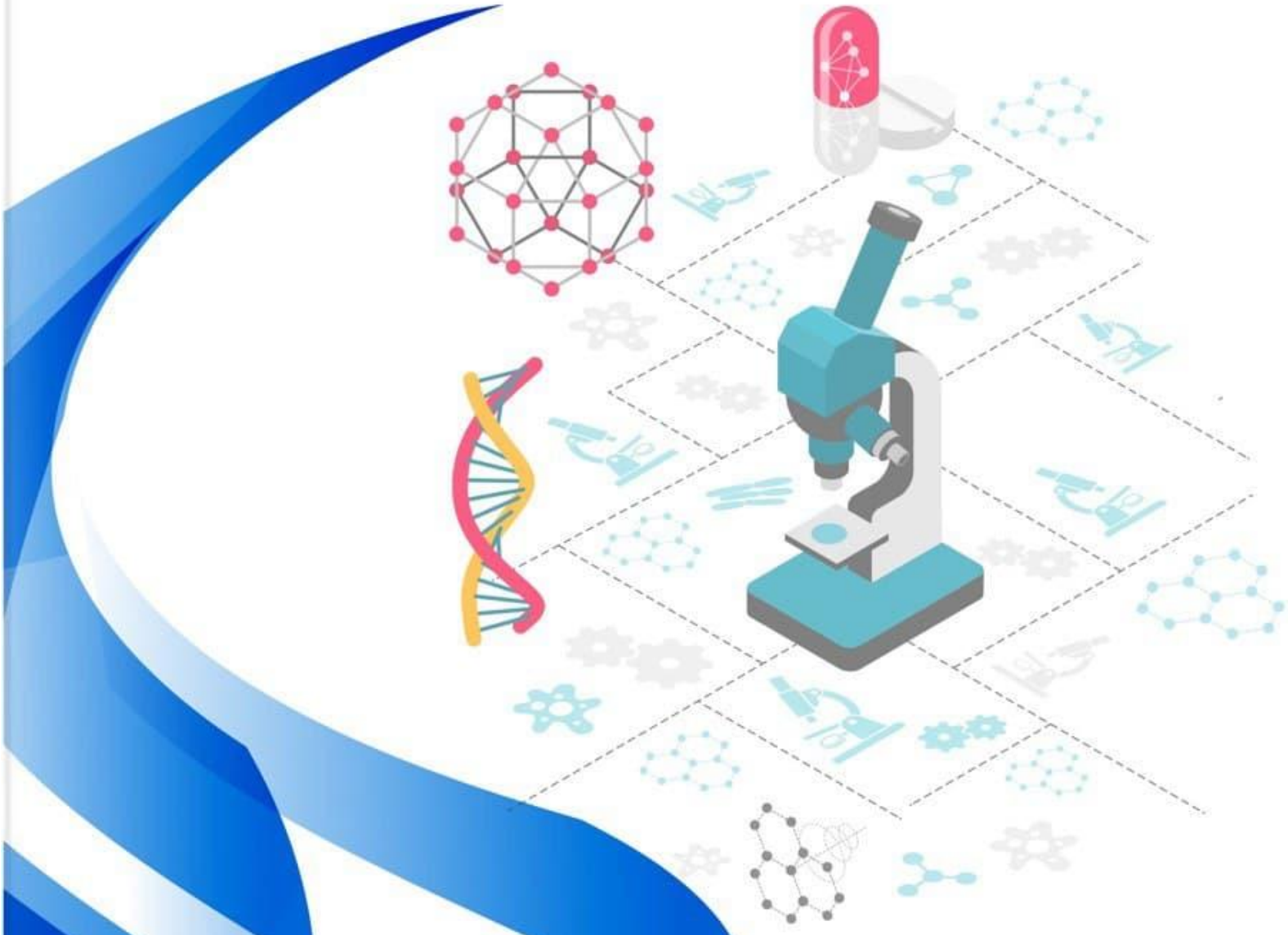

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INDICATORS OF LIPID METABOLISM IN PATIENTS WITH SARS-COV-2 INFECTION

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Abstract. The aim of the study was to analyze the published results of determining the parameters of lipid metabolism in patients with COVID-19 and convalescents. Material and methods. The articles were searched in the PubMed, Elsevier, Scopus, Google Scholar, eLIBRARY databases for the period from 2019 to 2023 using the keywords: lipid profile, cholesterol, triglycerides, COVID-19, SARS-CoV-2, multiple organ failure, disease severity, mortality. A total of 134 publications were found, 54 full-text articles with the results of clinical, randomized and cohort studies, 5 systematic reviews and 4 meta-analyses were selected for analysis. Results and discussion. Multidirectional changes in lipid profile parameters were established in patients with COVID-19 and in the postcovid period. Low levels of high-density lipoproteins (HDL), before SARS-CoV-2 infection have been observed in patients with severe COVID-19. Low HDL and apolipoprotein A-I levels increase the risk of COVID-19 disease. Monitoring lipid/lipoprotein levels can predict the severity of the disease. Patients with COVID-19 with low levels of LDL and/or HDL have an increased risk of developing severe course of the disease with higher mortality. An increase in lipoprotein (a) levels may be a marker of the possible development of complications, especially thromboticones. In the postcovid period, there is a risk of developing dyslipidemia. Conclusion. Hypolipidemic drugs (PCSK9 inhibitors and omega-3 fatty acids) may be recommended in the complex treatment of COVID-19.

Keywords: COVID-19, dyslipidemia, obesity, treatment, lipoproteins, statins, fibrates.

Introduction. Infectious and inflammatory reactions significantly modify the metabolism of lipids and lipoproteins. Plasma triglyceride levels increase as a result of increased secretion of very low density lipoproteins (VLDL), lipolysis of adipose tissue, activation of de novo synthesis of fatty acids in the liver and suppression of their oxidation [1-4]. In severe infectious and inflammatory diseases, hypercholesterolemia is explained by a decrease in VLDL clearance, a decrease in lipoprotein lipase activity, apolipoprotein E levels, activation of cholesterol metabolism in the liver and its secretion into bile [5]. Pronounced changes in proteins involved in the synthesis of high-density lipoproteins (HDL) lead to an increase in the delivery of cholesterol to immunocompetent cells. The oxidation of low-density lipoproteins (LDL) and very low-density lipoproteins is enhanced. HDL become pro-inflammatory molecules. They bind to ceramides, glucosylceramide and sphingomyelin, which promotes the activation of macrophage phagocytosis [6]. Metabolic processes involving lipoproteins, modified by the infectious and inflammatory process, initially protect the body from the harmful effects of viruses, bacteria and fungi. In the long-term or severe course of the disease, changes in the

level, structure and functions of lipoproteins can contribute to systemic atherogenesis and worsen the course of the disease [7]. The details of these biochemical reactions in patients with SARS-CoV-2 infection have not been sufficiently studied, which actualizes the research topic.

The aim of the work is to analyze the published results of determining the parameters of lipid metabolism in patients with COVID-19 and convalescents.

Material and methods. The analysis of full-text publications of the results of clinical, randomized and cohort studies, systematic reviews and meta-analyses from scientific databases PubMed, Elsevier, Scopus, Google Scholar, eLibrary from 2019 to 2023 by search queries: lipid profile, cholesterol, triglycerides, COVID-19, SARS-CoV-2, multiple organ failure, severity of course diseases, mortality. A total of 134 publications were found. 54 full-text articles with the results of clinical randomized and cohort studies, 5 systematic reviews, 4 meta-analyses and 12 thematic reviews (based on data from clinical randomized trials and systematic reviews) were selected for analysis. Works describing single observations and not related to the chosen topic are excluded from the total number.

Probable factors of dyslipidemia development in SARS-CoV-2 infection

In patients with SARS-CoV-2 infection in severe and critical condition, high mortality is associated with the development of multiple organ failure and septic shock [1]. This category of patients, as a rule, has comorbid cardiovascular, bronchopulmonary pathology, chronic kidney and liver diseases and/or diabetes mellitus. Violation of lipid metabolism is one of the key links in the pathogenesis of all these conditions [2].

Dyslipidemia was observed in all patients infected with SARS-CoV-2, divided by age, race, gender, degree of obesity, smoking, presence of cardiovascular diseases, chronic kidney disease, diabetes and hypertension [1]. Published studies describe lipid metabolism disorders that were most often detected in severe COVID-19 with multiple organ failure [3]: a decrease in triglycerides (TG), total cholesterol (OH), HDL and LDL.

Cholesterol as a mediator of the interaction of the target cell receptor with the S protein of the SARS-CoV-2 virus plays an important role in infection with the COVID-19 pathogen. An increase in the cholesterol content in the membranes of target cells increases the intensity of SARS-CoV-2 invasion, contributing to the fusion of membranes and the successful penetration of the pathogen into the host body [4]. The levels of LDL, HDL, apolipoprotein (Apo) A-I, Apo A-II and Apo B, TG may vary due to differences in the diet of patients, timing of blood sampling, taking medications (glucocorticoids, propofol) and the presence of comorbid diseases (diabetes mellitus), which can affect the lipid profile profile [5].

In a meta-analysis by A. Zinelu et al., serum concentrations of OH, LDL and HDL were significantly lower in patients with severe COVID-19, who were observed in the intensive care unit and with a fatal outcome of the disease in comparison with surviving patients with mild forms of the disease. There was no connection between

the above indicators of lipid metabolism and changes in serum TSH concentration [6].

When infected with the human immunodeficiency virus (HIV), a significant decrease in serum HDL concentrations is associated with impaired function of the ATP-binding transporter A1-dependent cholesterol transport from macrophages and activation of endothelial lipase and phospholipase A2 mediated by proinflammatory mediators [7]. In patients with COVID-19, changes in these transport systems and enzymes have not yet been studied in detail. It is possible that other mechanisms may also be involved in this disease.

Hypercholesterolemia in severe COVID-19 is partially explained by the use of cholesterol to form a surfactant during virus replication in the lungs and/or by a decrease in cholesterol synthesis during the development of liver failure [8]. This aspect is indirectly confirmed by the study of A. Zinellu et al., which found that a low concentration of serum prealbumin, a combined marker of inflammation and malnutrition, is largely associated with the severe course of COVID-19 and adverse clinical outcomes [9].

The results of the studies proved a decrease in the content of HDL, especially their small fractions, and the predominance of small LDL fractions in SARS-CoV-2 infection [10]. As with other infectious diseases, the composition of HDL changes with COVID-19 with a decrease in the titers of Apo A-I, A-II, paraoxonase, protein B, interconnected with pulmonary surfactant, and an increase in the content of serum amyloid A and alpha-1 antitrypsin [11]. Cholesterol elimination and the antioxidant capacity of serum apolipoprotein B are also reduced in patients with COVID-19 [12].

Viremia and toxemia in COVID-19 can lead to changes in the lipid profile due to activation of specific proinflammatory cytokines and/or increased expression of the type 1 class B capture receptor [13]. The concentration of tumor necrosis factor and interleukins (IL) 1 and 6 increases during infectious diseases, including COVID-19, which leads to changes in the lipid profile [14].

Lipoproteins

The pathophysiology of lowering LDL levels during infectious diseases has not been studied in detail, since in experimental models (in rodents) infection with hepatitis B virus leads to an increase, and in humans – to a decrease in this parameter [14]. This fact is probably explained by differences in the initial LDL concentration: in humans, it is much higher than in rodents. Due to the lack of an adequate experimental model, most studies were conducted in vitro using human hepatoma HepG2 cells. It has been proven that various cytokines reduce cholesterol levels, synthesis and secretion of Apo B by HepG2 cells [15]. Cytokines increase the activity of LDL receptors in human hepatocytes, which helps to reduce the content of lipoproteins in blood serum, but whether these changes occur in vivo with COVID-19 in humans is not reliably known [16]. The enzyme proprotein convertase subtilisin kexin type 9 (PCSK9) can enhance the degradation of LDL receptors and affect the clearance and content of lipoproteins in blood serum. However, the concentration of

PCSK9 does not change in patients with COVID-19, so a change in PCSK9 levels does not explain the decrease in LDL in this category of patients [17].

Reduction of HDL levels during infectious diseases is a multifactorial process that depends on the type, severity of infection, time of measurement and initial parameters of the individual's blood serum. In severe and/or prolonged course of infectious and inflammatory diseases (sepsis, infectious endocarditis, pneumonia), HDL actively reacts with ceramides, glucosylceramide and sphingomyelin. The resulting cytokines have immunomodulatory properties, stimulating macrophage phagocytosis, reducing apoptosis of immunocompetent cells [14]. A decrease in HDL levels in blood serum is discussed as a possible parameter for predicting adverse clinical outcomes in patients with infectious endocarditis and sepsis [18].

Triglycerides

A number of metabolic changes in infectious diseases can lead to an increase or normalization of TSH levels, despite changes in food intake [14]. An increase in the content of fatty acids due to their de novo synthesis in the liver, an increase in lipolysis of adipose tissue with activation of fatty acid transport to the liver, a decrease in their oxidation and secretion by VLDL hepatocytes, as well as a decrease in lipoprotein clearance lead to an increase in TSH levels [19]. Together, these processes increase the availability of fatty acids for the synthesis of TG, the formation and secretion of VLDL. Cytokines, in addition to stimulating the formation of VLDL, reduce the activity of lipoprotein lipase, a key enzyme that metabolizes lipoproteins. Inflammatory reactions lead to the activation of angiopoietin-like protein 4, an inhibitor of lipoprotein lipase activity, which blocks lipoprotein metabolism [20].

Lipoprotein (a)

Synthesis of apolipoprotein (a), a key protein component, increases during a prolonged or severe course of an infectious and inflammatory disease (infectious endocarditis, sepsis) [14]. IL-6 stimulates the synthesis of apolipoprotein (a) in several variants [21]. The antibody inhibiting IL-6, tocilizumab, reduces the level of lipoprotein (a) [22]. It is likely that in infections accompanied by a prolonged increase in IL-6 levels, lipoprotein (a) levels also increase.

The relationship of lipid profile parameters with the risk of infection, the development of multiple organ pathology and death in COVID-19

During cohort studies, it was found that a decrease in LDL and/or HDL serum levels increased the risk of infection with infectious agents and the development of disease, for example community-acquired sepsis [23, 24]. In patients with end-stage renal failure, low LDL and HDL levels were associated with a higher risk of death from infection [25]. During the COVID-19 pandemic, several studies were conducted examining the effect of lipid/lipoprotein levels on the risk of COVID-19. Studies using the UK biobank and other large databases have shown that a decrease in HDL and Apo A-I levels, measured many years before the pandemic, was associated with an increased risk of infection, severe course, multiple organ failure and death in

COVID-19, especially in people over 75 years of age [26]. The initial content of LDL, Apo B, lipoprotein (a) and TG was not associated with an increased risk of SARS-CoV-2 infection. A decrease in HDL by 0.26 mmol/l (10 mg/dl) or a decrease in Apo A-I by 10 mg/dl was associated with an increased risk of severe COVID-19 by about 10% [27].

Lipoproteins can bind and neutralize many different viruses. It should be particularly noted that HDL has antiviral activity against some RNA and DNA viruses, depending on the presence or absence of a shell, for example, in pneumonia associated with COVID-19 [28]. Bronchopulmonary or gastrointestinal diseases with a subclinical course can lead to a decrease in HDL and/or LDL and, consequently, to an increased risk of infection with SARS-CoV-2. In a study by Q. Feng et al. low LDL levels significantly correlated with an increased risk of sepsis and hospitalization in the intensive care unit in patients with infectious diseases, this relationship was due, among other things, to the development of multiple organ pathology in the observed [29].

Genetically determined lipid levels and the risk of COVID-19 disease

In a prospective cohort study involving about 100 thousand people, 2 common variants of genes encoding liver lipase and cholesterol ester transfer protein, which regulate HDL levels, were studied. S. Madsen et al. It was found that low and high HDL levels can increase the risk of COVID-19 infection [30].

In a study of material from the UK biobank, taken from more than 400 thousand people, M. Trinder et al. It has been proven that a reduced level of polygenic LDL indicators associated with low HDL content increases the risk of hospitalization of patients with gastroenteritis, pneumonia, diseases of the urinary system, skin of bacterial and viral etiology, acute kidney damage and fatal outcomes in sepsis. These clinical parameters are not affected by the association of polygenic LDL parameters with TG [31]. In a study by M. Trinder et al. There was no correlation between an increase in HDL content by 1 mmol/l and the risk of infection with bacterial, viral and fungal diseases of any localization. The authors, using data from 7 different cohorts, proved that the level of cholesterol ester transfer protein, which increases HDL levels, correlated with a decrease in the risk of infection with this infectious pathology. At the same time, variants of the cholesterol ester transfer protein that reduce the HDL content were interrelated with an increased risk of developing infectious diseases of various localization. Genetic variants of 3 hydroxy-3-methylglutaryl coenzyme A reductase (HMGCoA reductase), which is a transmembrane protein and catalyzes a key step in the synthesis of mevalonic acid (a precursor of sterols, isoprenoids and other lipids) and PCSK9, which reduce LDL levels, were not associated with an increase in mortality in sepsis. The results of these studies suggest that it is a decrease in HDL levels that is associated with the risk of severe infections [31].

An analysis of published data on the relationship of genetically determined levels of cholesterol, apolipoprotein B, TG and LDL with the risk of infection with SARS-CoV-2 showed that they turned out to be contradictory [32-35].

The indicator of genetically dependent levels of lipoprotein (a) concentration was the same in the control group and in patients with COVID-19 [36]. It has been established that Apo E4/4 homozygosity is interrelated with a 2-3-fold increased risk of SARS-CoV-2 infection, although the pathogenetic mechanism linking these aspects has not yet been established [37]. Additional studies are needed to identify the presence or absence of correlations of genetically determined lipid/lipoprotein levels with the risk of COVID-19, as well as to clarify the pathophysiology of these relationships.

Lipid profile indicators as prognostic criteria for the severity of COVID-19

As prognostic criteria for the severity of the clinical course and outcomes of COVID-19, indicators of systemic inflammation, lipid profile and ratios of TG/HDL, OH/HDL, LDL/HDL parameters, the number of blood leukocytes/HDL and serum glucose/HDL levels were studied. In a study by J. Muhammadshahi et al. It was proved that in deceased patients, the values of TG, OH, LDL and HDL, as well as the ratio of OH/HDL, LDL/HDL, TG/HDL, lymphocytes/HDL and HDL monocytes were significantly lower, and the ratio of leukocytes/HDL and hemoglobin/HDL was higher than in recovered patients. A reliable relationship between the estimated parameters and the adverse outcomes of COVID-19 disease has been proven [38].

The severity of COVID-19 is directly correlated with a decrease in OH, LDL and HDL levels [39]. High levels of C-reactive protein (CRP), a marker of immuno-inflammatory reactions, are correlated with low levels of LDL and HDL [40]. Low levels of LDL and/or HDL upon admission to the hospital are defined as prognostic criteria for an increased risk of severe course and death from COVID-19. Also, a decrease in the content of OH, HDL and LDL against the background of COVID-19 is associated with the severity of the disease and death [39]. Two meta-analyses did not reveal a relationship between the concentration of TG and the severity of COVID-19 [6, 41].

Lipoprotein (a) levels are predominantly genetically determined and very heterogeneous with 200-fold differences between individuals. In a small study, no increase in lipoprotein (a) levels was found in patients with COVID-19 compared with those observed in the control group. However, studies have shown that an increased content of lipoprotein (a) is associated with a severe course of the disease [42]. Lipoprotein (a) levels may increase in those hospitalized with COVID-19, which is associated with a high risk of thrombotic complications. An increase in lipoprotein (a) content is associated with an increase in IL-6 levels and is not related to the content of CRP [43]. If further studies demonstrate a strong correlation between the concentration of lipoprotein (a) and IL-6, then it is possible to consider the possibility of drug action to reduce the concentration of lipoprotein (a), which may lead to a decrease in the number of complications in COVID-19.

As with other infectious diseases, recovery in COVID-19 is associated with a return of lipid/lipoprotein levels to baseline values. It was found that a few months after recovery, patients in the postcovid period have an increased risk of dyslipidemia with an increase in the concentration of OH, LDL and TG and a decrease in HDL. After infection with SARS-CoV-2, increases in OH >5.17 mmol/L (200 mg/dl) [risk ratio (HR) 1.26; 95% confidence interval (CI) 1.22–1.29], TG >2.26 mmol/L (150 mg/dl) (HR 1.27; 95% CI 1.23–1.31), LDL cholesterol >3.36 mmol/L (130 mg/dl) (HR 1.24; 95% CI 1.20–1.29) and HDL >1.03 mmol/L (40 mg/dl) (HR 1.20; 95% CI 1.16–1.25) in patients with COVID-19 compared to the control group were not observed [44].

The use of lipid-lowering drugs in patients with COVID-19 A systematic review and meta-analysis of European and North American studies involving 2,398 patients with COVID–19 confirmed that the use of statins is associated with a significant reduction in the risk of disease progression and death in COVID-19 [odds ratio (OR) 0.59; 95% CI 0.35-0.99, p=0.02] [45]. Many of the widely used lipid-lowering drugs have a pleiotropic effect, which should be taken into account in the treatment of COVID-19. For example, statins reduce inflammation, oxidative stress, endothelial dysfunction, and PCSK9 activity [46]. These advantages have aroused interest in analyzing the effect of lipid-lowering drugs on the course of SARS-CoV-2 infection. Studies have shown that in patients taking statins, the severity of COVID-19 and the frequency of deaths decrease [47]. However, 3 out of 4 published randomized trials did not reveal significant positive effects of statin use in patients with SARS-CoV-2 infection [48]. It is noteworthy that no toxic effects were detected in patients with statin therapy. Obviously, additional analysis is required, which is why many randomized trials are currently being conducted. Patients receiving nirmatrelvir and ritonavir, due to drug interactions, should avoid treatment with atorvastatin, simvastatin and lovastatin, since they are metabolized with the participation of cytochrome CYP3A4. In this group of patients, it is advisable to use low doses of rosuvastatin [49, 50].

Currently, the results of randomized trials on the use of statins in COVID-19 patients are available. In particular, taking 2 g of docosahexaenoic + eicosapentaenoic acids for 2 weeks in a randomized trial involving 30 patients revealed relief of some symptoms of infection, such as body pain, fatigue and decreased appetite [51].

The results of a double-blind randomized trial involving 128 critically ill patients showed that treatment with 400 mg of eicosapentaenoic acid and 200 mg of docosahexaenoic acid for 14 days was associated with a significant improvement in survival (21% in the eicosapentaenoic acid/docosahexaenoic acid group versus 3% in the control, p=0.003) [52]. A randomized open trial involving 100 outpatient patients with COVID-19 who received icozapent ethyl (purified eicosapentaenoic acid) 8 g daily for 3 days, then 4 g daily for 11 days, proved symptom relief compared with conventional treatment in the control group [53]. The mechanism of the positive effect of the use of PCSK9 and omega-3 fatty acid inhibitors in patients with

COVID-19 has not been established in detail. The results of a randomized trial did not reveal a significant improvement in the condition of patients with COVID-19 treated with fenofibrate compared with patients in the control group [54]. No randomized studies have been found to determine whether the following drugs with lipid-lowering effects have a beneficial effect in SARS-CoV–2 infection: ezetimibe is a selective inhibitor of the absorption of cholesterol and some plant styrene in the small intestine; niacin is nicotinic acid, a B vitamin that reduces the concentration of total cholesterol, apolipoprotein A, triglycerides, LDL and increases HDL levels; bile acid sequestrants that bind cholesterol and bile acids synthesized in the liver; bempedoic acid is an inhibitor of adenosine triphosphate citrate lyase, suppressing cholesterol biosynthesis and reducing LDL cholesterol in the blood through stimulation LDL-receptor; inclisiran, which inhibits the synthesis of a protein that increases LDL levels in the blood. These drugs are currently a target for research, since their mechanism of action can affect the lipid profile of patients with SARS-CoV-2 infection.

Dyslipidemia in bridge syndrome has been recognized by the World Health Organization (WHO) as a condition after COVID-19 or long-term COVID pathology, "which occurs in people with a previous history of probable or confirmed SARS CoV-2 infection, usually 3 months after onset, with symptoms lasting at least 2 months, which cannot be explained an alternative diagnosis" (Delphi consensus) [55]. The pathophysiology of the process is interrelated with organ damage due to an active inflammatory reaction caused by the SARS-CoV-2 virus, its persistent persistence and reactivation in certain tissues as a result of impaired immunity, concomitant infectious diseases, including Epstein-Barr virus infection [56], changes in the host microbiome, coagulopathy, autoimmune reactions due tofor molecular mimicry between SARS-CoV-2 and autoantibodies [57-61].

In bridge syndrome, dyslipidemia is observed in the pool of sterols, steroids and fatty acid esters. V. Guntur et al. [62] revealed higher levels of polyunsaturated fatty acids in this category of observed patients, which is consistent with a decrease in fatty acid oxidation at the mitochondrial level and is interrelated with erythrocyte dysfunction, impaired oxygen transfer. The detected changes in lipid composition may persist for several months, which may explain symptoms such as fatigue and exercise intolerance.

A systematic review and meta-analysis have proven that low concentrations of HDL and LDL are significantly correlated with the severity of the course and mortality in COVID-19, and this suggests that cholesterol concentrations can be used to stratify the risk of an adverse course of this pathology and monitor patients [6].

V. Ghini et al. [63] found that the lipid profile of patients who recovered from SARS-CoV-2 infection slowly returned to normal levels.

In patients with COVID-19, changes in the content of bile acids have been demonstrated, which can affect immuno-inflammatory, metabolic processes and intestinal microbiota [64]. Intestinal dysbiosis can contribute to the development of

the inflammatory process [65]. Impaired bile acid metabolism is associated with damage to liver tissue, which affects the substance transport system (cholesterol transport). These facts increase the risk of developing severe COVID-19 [66]. A violation of bile acid metabolism was detected 3 months after recovery from COVID-19, and this suggests that pathological processes at the level of the intestinal mucosa are disrupted before complete recovery and recovery occurs [67].

Violations of the isoprenoid pathway (mevalonate or HMG-CoA reductase) have been proven in patients who have undergone COVID-19. Isoprenoids are a diverse class of biomolecules, including cholesterol, vitamin K, coenzyme Q10, and all steroid hormones [68]. The mevalonate pathway blocks the activation of inflammasomes and the release of cytokines, and inadequate signaling may be associated with the pathophysiology of COVID-19. The study revealed a violation of the regulation of genes involved in the mevalonate pathway exclusively in SARS-CoV-2 infection [69]. The use of statins, namely HMG-CoA reductase inhibitors, in the treatment of COVID-19 reduces cholesterol levels and virus titers due to immunomodulatory, anti-inflammatory and antithrombotic effects [70].

In patients who underwent COVID-19, a change in the content of polyunsaturated fatty acids – arachidonic and linoleic [71] was revealed. F. Li et al. [72] described a violation of lipid metabolism (TG, LTB4, prostaglandin E2, polyunsaturated fatty acids 5 hydroxyeicosotetraenoic, 12 hydroxyeicosatetraenoic and 15-oxoeicosatetraenoic) 6 months after discharge in patients with COVID-19 and associated it with immune dysregulation. There was an increase in the concentration of glycerophospholipids and sphingolipids in blood serum in recovered patients [72].

Sphingolipids are an important group of biologically active molecules involved in processes such as inflammatory reactions, cell differentiation, regeneration, aging, as well as the most important in the cells of the musculoskeletal system [73]. Dysregulation of sphingolipid metabolism may be associated with fatigue and muscle pain in bridge syndrome [74]. In COVID-19 patients, changes in the content of phosphatidylcholines were detected and they depended on the severity of the disease [75].

Conclusion

The analysis of published materials on the problem of lipid metabolism allows us to state that there are multidirectional changes in the lipid profile in patients with COVID-19 and in the post-ovoid period. Low HDL levels before SARSCoV-2 infection are noted in patients with severe COVID-19. Low HDL and apolipoprotein A-I levels increase the risk of COVID-19 disease.

With the development of the COVID-19 infectious process, lipid/lipoprotein levels change, and monitoring of these indicators makes it possible to predict the severity of the disease. Patients with COVID-19 with low levels of LDL and/or HDL have an increased risk of developing a severe course of the disease and a higher incidence of deaths. An increase in lipoprotein (a) content may be a marker of the

possible development of complications, especially thrombotic ones. After recovering from COVID-19, patients may also have a higher risk of developing dyslipidemia.

Lipid-lowering drugs, especially PCSK9 inhibitors and omega-3 fatty acids, may be recommended in the treatment of COVID-19, as they have positive pleiotropic effects.

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