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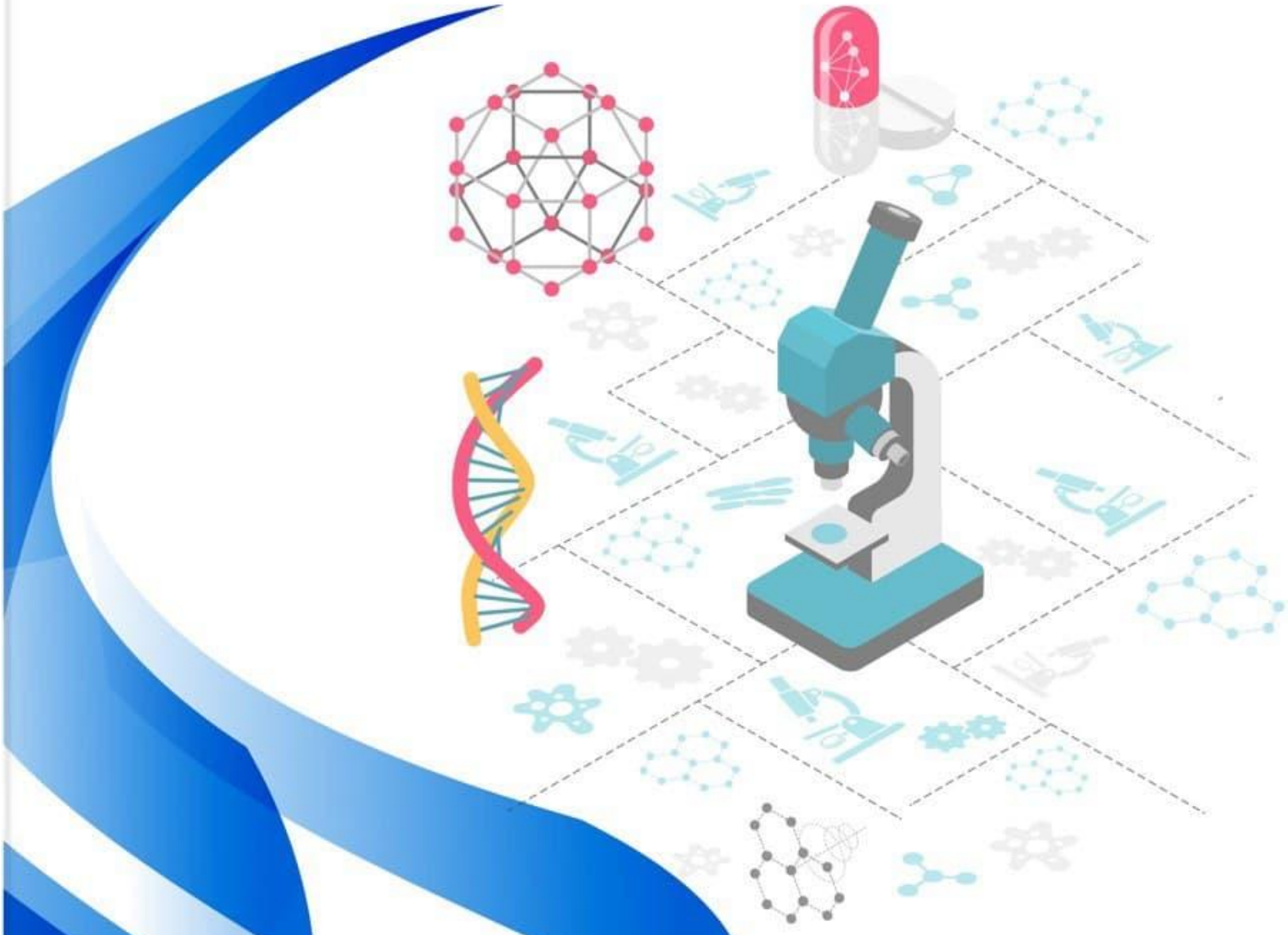

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COVID-19 AND DYSLIPIDEMIA

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Resume. The COVID- 19 pandemic is a global problem for both the management of patients with acute disease and post-cystic complications. Against the background of COVID-19, the development of systemic inflammation is often observed, accompanied by a "cytokine storm", hemostasis disorders and severe vasculitis. New evidence suggests that impaired regulation of lipid metabolism may contribute to the development of these complications. This review summarizes the latest information on the potential mechanisms associated with dyslipidemia against the background of COVID-19. In particular, it has been suggested that changes in the amount and composition of high-density lipoproteins (HDL) in COVID-19 may significantly weaken the anti-inflammatory and antioxidant effects of HDL and contribute to inflammation in the lungs. In addition, it has been hypothesized that lipoproteins with oxidized phospholipids and fatty acids can lead to viral organ damage due to hyperactivation of scavenger receptors ("scavenger receptors") of innate immunity.

Keywords: COVID-19, dyslipidemia, cytokine storm, vasculitis.

Introduction. The clinical manifestations of COVID-19 range from asymptomatic to severe pneumonia, leading to acute respiratory distress syndrome (ARDS) and cardiogenic shock, especially among elderly patients with concomitant chronic diseases [1, 2]. Violations of the regulation of acquired immunity against the background of aging or chronic systemic metabolic disorders can lead to a decrease in the tolerance of viral infections [3]. Hyperlipidemia and hyperglycemia are known to reduce the immune response and can lead to persistent chronic inflammation, which increases the risk of cardiovascular diseases (CVD) [4, 5]. In addition, increased metabolic needs in acute inflammation caused by viral infection leads to a decrease in myocardial oxygenation, ischemic damage and vascular dysfunction with thrombotic complications [4]. Thus, it is obvious that traditional CVD risk factors can significantly contribute to morbidity and mortality from SARS-CoV-2 infection.

Changes in lipoproteins in COVID- 19

The control of plasma lipids and lipoproteins is an important part of the modern approach to risk management of cardiovascular diseases. Low HDL levels are a predictor of the occurrence and progression of CVD [6, 7] and serve as a biomarker of an increased risk of mortality from all causes, as well as the occurrence of nonfatal myocardial infarction, even in patients taking statins [8]. The most studied function of HDL is the reverse transport of cholesterol (OTC) from tissues to the liver [9]. In addition to their function in OTC, HDL particles have a number of other properties that can participate in the modulation of the immune system and the fight against infectious diseases. In particular, HDL particles have the property of binding and neutralizing pathogen-associated lipids (for example, lipopolysaccharide,

lipoteichoic acid), which mediate excessive activation of the immune system in sepsis. HDL particles also have immunomodulatory, antithrombotic and antioxidant effects [10]. For example, HDL levels have been shown to be inversely proportional to the frequency of some autoimmune diseases [11].

High-density lipoproteins are a heterogeneous set of particles of different sizes and apolipoprotein composition. ApoA-I is the main protein in HDL, it is present in most HDL particles, whereas other apolipoproteins, such as ApoE, are associated with specific HDL subspecies. The transport of cellular cholesterol is mainly due to the interaction between relatively ApoA-I-poor lipids in small discoid (pre- beta) forms of HDL and cellular carriers (for example, ABCA1, ABCG1 and SR-BI).

The SARS-CoV-2 virus binds to angiotensin converting enzyme 2 (ACE2) through S-proteins, which facilitate its entry into the cell, followed by damage by alveolar macrophages. The tissue microenvironment releases pro-inflammatory cytokines and chemokines (IL-6, MCP1 and MIP), which promote the attraction of macrophages, neutrophils and T cells. This activation of cells leads to uncontrolled inflammation and dysregulation of immune responses with further accumulation of eicosanoids such as PGE2, TXB2, LTB4 and LXA4. Persistent inflammation culminates in the modulation of HDL-related apolipoproteins, for example, in a decrease in the level of apolipoprotein A-I (ApoA-I), ApoE and an increase in serum amyloid protein A, which negatively affects the anti-inflammatory, antioxidant and immunomodulatory functions of HDL. An imbalance in the antioxidant system also causes modification of LDLP through the intracellular lectin-like receptor of LDLP (LOX-1). The extracellular part of LOX-1, soluble in serum (sLOX-1), additionally stimulates the interaction between oxidized lipids and circulating macrophages, which leads to the release of proinflammatory cytokines such as IL-6, IL-10 and tumor necrosis factor α (TNF-α). Impaired function of paraoxonase 1 (PON1) on HDL and an excessive inflammatory reaction lead to further lipid oxidation. Excessive formation of LDL and HDL leads to a change in lipoprotein transport and disruption of the reverse cholesterol transport pathway (RCT) (shown on the left), characterized by insufficient interaction of ApoA-I with adenosine triphosphate-binding transporter A1 (ABCA1) on macrophages and a decrease in cholesterol esterification lecithin-cholesterol-acyltransferase (LCAT). This leads to a decrease in the return of cholesterol esters to the liver either directly after interaction with hepatic scavenger receptors-B1 (SR-B1), or indirectly after transfer to HDL by the cholesterol ester transporter protein (CETP) and absorption by hepatic LDL receptors (LDL-R). Low levels of ApoE and ApoC-III on HDL lead to a decrease in lipoprotein lipase (LPL) activity, which in turn leads to the accumulation of LDL and TG.

HDL-related apolipoproteins such as apolipoprotein A-I (ApoA-I) and apolipoprotein M (ApoM) interact with lipid rafts on cell membranes rich in immune cell receptors, such as Toll-like receptors (TLR) on macrophages [12] and T-cell receptors [13], and modulate the immune response. It is noteworthy that early and later literature suggested the presence of a feedback link between HDL and the risk of

hospitalization for an infectious disease [14]. It is also known that the anti-inflammatory and antioxidant properties of HDL are significantly reduced during influenza [15] and HIV infection [16]. Indeed, lower levels of both HDL and LDL were found in HIV patients, which recovered after treatment [12]. In the context of COVID-19, it has recently been reported that low levels of total cholesterol (OHC), HDL-C and LDL-C are associated with disease severity and mortality [17, 18]. Elevated plasma triglyceride levels during infection and inflammation are also a well-known phenomenon [14, 19].

The mechanisms by which increased inflammation reduces HDL functionality are not precisely defined. It has previously been observed that inflammation alters the composition of HDL apolipoproteins. It was noted that inflammation alters the expression of apolipoprotein genes in the liver [20] and promotes the binding of proinflammatory serum amyloid protein A (SAA), which, in turn, replaces and reduces the levels of ApoA-I in HDL [21]. In addition, in conditions of acute inflammation, reduced levels of lecithin cholesterol acyltransferase (LCAT) in plasma can also alter HDL function and further disrupt the inflammatory response [22]. Interestingly, a recent study showed that HDL under the action of ex vivo HCT reduces the amount of HDL-bound SAA, while simultaneously increasing the amount of HDL-bound ApoA-I and HDL function [23]. It has recently been shown that plasma SAA levels dynamically increase depending on the severity of COVID-19, and SAA has been promoted to the role of a biomarker for assessing the severity and prognosis of COVID-19 [24]. Together, these results suggest that the composition and functions of HDL in patients with COVID-19 are changing, and interventions aimed at their recovery can improve HDL function and reduce the burden of the disease.

Other mechanisms leading to HDL dysfunction include oxidative modification of ApoA-I on the background of inflammation, which reduces OTC [25]. Paraoxonase 1 (PON1), an antioxidant enzyme present in HDL, is also inactivated during oxidative stress caused by inflammation [26], which further impairs HDL function. In practice, low PON1 activity is associated with a deterioration in the prognosis of cardiovascular diseases, and it has been found to decrease in various inflammatory [27] and infectious [28] diseases. IL-10, which under certain circumstances can act as a pro-inflammatory cytokine, can also reduce HDL levels in plasma [44] by increasing micropinocytosis [29].

Violation of the antioxidant activity of HDL additionally leads to the oxidation of lipids, in particular, to the formation of oxidized LDL. As discussed below, oxidized LDL and HDL are powerful activators of "wiper" receptors for the removal of oxidized LDL, which cause increased inflammation and aggravation of tissue damage.

ApoE and COVID - 19

In addition to ApoA-I, ApoE is also found among HDL, as well as in lipoproteins containing apoB. ApoE serves as a ligand for the clearance of

triglyceride-rich lipoproteins apoB-containing lipoproteins by binding to receptors of membrane lipoproteins from the LDL receptor family [30-33]. The most common isoform, ApoE3, has Cys in codon 112 and Arg in codon 158. The ApoE2 isoform (Arg158Cys) is associated with a decrease in LDL levels, whereas the ApoE4 isoform (Cys112Arg) is associated with elevated plasma LDL levels and Alzheimer's disease [30]. ApoE deficiency in humans leads to an increase in plasma triglycerides and cholesterol in apoB-containing lipoproteins, a decrease in HDL levels, palmar tuberculous xanthoma and premature cardiovascular diseases [34, 35]. It is well known that the absence of ApoE in knockout mice leads to atherogenesis against the background of low HDL levels and high levels of TG-rich lipoproteins [36]. It has been shown that increasing the activity of both ApoE and phospholipid transporter protein improves the delivery of energy substrates and phospholipids to tissues, which contributes to maintaining cell membrane homeostasis in intensive care patients [37].

In addition to delivering apoB lipoprotein to cells, ApoE has additional functions. Thus, it has been shown that through its receptor-binding domain, it protects LDL from oxidation [56] and can also participate in OTC [38]. ApoE-containing HDL promotes the outflow of cholesterol from extrahepatic cells [39] through ABCA1- and ABCG1-dependent processes, and this mechanism is counteracted by the presence of ApoC-III [40]. ApoE is also expressed and secreted by monocytes and macrophages with anti-atherosclerotic action, it is also present in other tissues such as adipose tissue, brain, kidneys and adrenal glands [30, 41]. It was noted that despite the fact that the vascular endothelium does not produce ApoE, local expression of this protein by macrophages has a paracrine effect on the endothelium, leading to inhibition of VCAM-1, stimulation of NO production, suppression of endothelial activation and reduction of monocyte adhesion to the endothelium, whereas ApoE4 counteracts these anti-inflammatory effects [30].

Some evidence suggests that deficiency of ApoE function in SARS-CoV-2 dyslipidemia may contribute to the progression of the disease and the development of complications. It is noteworthy that ApoE is expressed in lung macrophages and alveolar epithelial cells (both type I and type II) [42]. ApoE knockout mice are very susceptible to acute lung damage due to an IL-6-dependent mechanism that increases the permeability of endothelial cells to oxidized LDL [43]; IL-6 is well known to be the main cytokine released during the "cytokine storm" in COVID-19 [44]. In humans, ApoE can potentially act as an endogenous signal triggering the formation of NLRPS inflammasome in alveolar macrophages in asthma [45]. Moreover, the APOE gene is associated with the altered physiology of human lungs [46]. It has also been reported that the ApoE4 isoform may be a predictor of the severity of COVID-19. ApoE4/E4 homozygotes from the UK Biobank were more likely to be positive for COVID-19 (OR (OR) 2.31, CI (CI) 1.65–3.24, P = 1.19 × 106). The association between the ApoE4/E4 genotype and COVID-19 was independent of concomitant dementia, cardiovascular disease, or type 2 diabetes.

Oxidized lipoproteins and scavenger receptors in COVID - 19

Low-density lipoproteins are the main transport for the transfer of cholesterol and phospholipids into the bloodstream. During acute inflammation, LDL and its main apolipoprotein, apolipoprotein B (apoB), are oxidized (LDL). Lipid hydroperoxides derived from the lipoxygenase pathway [47] and acids derived from arachidonic acid and linoleic acid accumulate, and some of them are esterified into cholesterol esters, triacylglycerin and phospholipids in LDL [48]. Oxidized phospholipids (ohFL) in ohLPNP are recognized by scavenger receptors as damage-related molecular patterns (damps) and trigger a cascade of intracellular signaling events culminating in the activation of the inflammasome and dysfunction of endothelial cells, which contribute to the initiation and progression of atherosclerosis [49]. In addition, ohFL production increases in the lungs of people and animals infected with the virus, and ohFL induces cytokine production by macrophages and acute lung inflammation in mice [50].

Scavenger receptors, lectin-like LDL receptors expressed in endothelial cells, macrophages and smooth muscle cells, are capable of binding to several ligands, including LDL, HDL, C-reactive protein and glycated end products [51, 52]. The binding of LDLP to the lectin-like LDL receptor leads to the internalization of LDLP and their accumulation in cells, which is believed to contribute to the early development of atherosclerotic lesions. In addition, ligand binding to the lectin-like LDL receptor triggers intracellular signaling processes leading to the launch of proapoptotic, prooxidant and proinflammatory pathways, causing cellular dysfunction associated with atherosclerosis and an increased risk of cardiovascular diseases [51, 53]. Since the lectin-like LDL receptor binds to damaged lipids such as LDL and HDL, these receptors can be a key mediator of cardiovascular diseases, causing inflammatory growth of atheroma and eventually lead to erosion and plaque detachment [54].

The association of activation of the lectin-like LDL receptor with acute inflammatory conditions increases the likelihood that LOX-1 is also activated and will contribute to complications of COVID-19. Recent clinical data suggest that MERS-CoV-2 can cause a multisystem inflammatory syndrome in children resembling Kawasaki disease (KD) [55, 56]. These data suggest that MERS-CoV-2 infection can cause endothelial damage in many organs [56].

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