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COVID-19—Associated dyslipidemia: Implications for mechanism of impaired resolution and novel therapeutic approaches

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Abstract

The current coronavirus disease 2019 (COVID-19) pandemic presents a global challenge for managing acutely ill patients and complications from viral infection. Systemic inflammation accompanied by a "cytokine storm," hemostasis alterations and severe vasculitis have all been reported to occur with COVID-19, and emerging evidence suggests that dysregulation of lipid transport may contribute to some of these complications. Here, we aim to summarize the current understanding of the potential mechanisms related to COVID-19 dyslipidemia and propose possible adjunctive type therapeutic approaches that modulate lipids and lipoproteins. Specifically, we hypothesize that changes in the quantity and composition of high-density lipoprotein (HDL) that occurs with COVID-19 can significantly decrease the anti-inflammatory and anti-oxidative functions of HDL and could contribute to pulmonary inflammation. Furthermore, we propose that lipoproteins with oxidized phospholipids and fatty acids could lead to virus-associated organ damage via overactivation of innate immune scavenger receptors. Restoring lipoprotein function with ApoA-I raising agents or blocking relevant scavenger receptors with neutralizing antibodies could, therefore, be of value in the treatment of COVID-19. Finally, we discuss the role of omega-3 fatty acids transported by lipoproteins in generating specialized proresolving mediators and how together with anti-inflammatory drugs, they could decrease inflammation and thrombotic complications associated with COVID-19.

Abbreviations: ACE2, angiotensin-converting enzyme 2; ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ALI, acute lung injury; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LOX, lipoxygenase; LOX-1, lectin-like oxLDL receptor; MERS, Middle East respiratory syndrome; OxLDL, oxidized LDL; OxPLs, oxidized phospholipids; PON1, paraoxonase 1; RAAS, renin-Angiotensin-Aldosterone System; ROS, reactive oxygen species; SAA, serum amyloid protein A; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SPMs, specialized proresolving lipid mediators.

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KEYWORDS
COVID-19, dyslipidemia, inflammation, lipoproteins, oxidation

1 | INTRODUCTION

Severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) is one of the 36 coronaviruses in the family Coronaviridae, within the order Nidovirales that are known to cause respiratory or intestinal infections in humans and other animals.[1] In humans, SARS-CoV-2 infection causes acute lung injury (ALI) with rapid progression to acute respiratory distress syndrome (ARDS), leading to COVID-19 disease.[2] The American-European Consensus Conference recognized ARDS as an acute condition characterized by diffuse alveolar injury, bilateral pulmonary infiltrates, and severe hypoxemia in the absence of evidence for cardiogenic pulmonary edema.[3] It has long been recognized that ARDS due to viral infections is associated with alterations in the host immunological status, including decreases in circulating neutrophils, dendritic cell subsets, natural killer cells, CD4+ and CD8+ T lymphocytes, and B lymphocytes, and increased levels of pro-inflammatory cytokines.[1] Some of the locally produced chemokines, such as monocyte chemoattractant protein-1 (MCP1) and macrophage inflammatory proteins (MIPs) attract monocytes, macrophages, and T cells to the site of inflammation.[4] More recently, it has been suggested that overactivation of the immune system due to SARS-CoV-2 infection causes a surge of pro-inflammatory factors, referred to as "cytokine storm," resulting in host organ damage, such as lung damage, increased lung endothelial and epithelial permeability, impaired gas exchange and severe respiratory failure with a high mortality rate.[5,6]

Severe acute respiratory syndrome coronavirus 2 is an enveloped, nonsegmented, positive-sense, single-stranded RNA virus that enters the host cells through endocytosis or membrane fusion. The first step in viral entry of SARS-CoV-2 into host cells is binding of a viral envelope transmembrane glycoprotein, known as the SPIKE (S) protein, to a cell host cell membrane receptor-enzyme protein, namely the angiotensin-converting enzyme 2 (ACE2) protein.[7] Subsequently, host cell infection by SARS-CoV-2 results in ACE2 internalization and reduction of cell surface ACE2 enzymatic activity. It has been reported that ACE2 membrane protein is highly expressed on the mucosa of oral cavity[8] and lung epithelial cells,[9] which determines the initial tissue entry site of the virus. Of note, endothelial cells,[10] along with human heart pericytes[11] also have high expression of ACE2, which may explain the pathophysiological effects related to the cardio-pulmonary system. ACE2 is an important enzyme involved in modulation of the renin-angiotensin-aldosterone system (RAAS). ACE2 converts Angiotensin II (ANGII) to ANG1-7, which binds to MAS, a receptor that signals to reduce the activity of the ANGII receptor AT1.[12] Decreasing cell surface ACE2 results in both increased ANGII and overactivation of AT1 and reduction of ANG1-7, both of which could contribute to SARS-CoV-2 infection cardiopulmonary complications. Of note, because both classes of antihypertensive medicines, angiotensin-converting enzyme inhibitor (ACEi) and angiotensin II receptor blocker (ARB), are known to increase ACE2 levels, there has been some concern that the use of these medications may increase susceptibility to SARS-CoV-2 infection,[13] although more data are needed to clarify this issue.[14]

The clinical presentation for COVID-19 varies from asymptomatic cases to individuals with severe pneumonia associated with ARDS and cardiogenic shock, particularly in older patients with chronic comorbidities.[2,15] Adaptive immune dysregulation associated with aging or with chronic systemic dysmetabolic conditions may result in lower tolerability to viral infections.[16] Hyperlipidemia and diabetes are known to compromise the immune response, and can lead to a sustained chronic inflammatory state, which leads to high cardiovascular (CVD) risk.[17,18] Furthermore, increased metabolic demands due to virally induced acute inflammation results in decreased myocardial oxygenation and ischemic damage and vascular dysfunction, with thrombotic complications.[17] Thus, it appears that traditional CVD risk factors may significantly contribute to the morbidity and mortality from SARS-CoV-2 infection.

No drug has proven to be effective for the routine prevention and or management of most causes of ARDS. Early administration of corticosteroids to septic patients usually does not prevent the development of ARDS. Numerous other pharmacologic therapies, including the use of inhaled synthetic surfactant, intravenous antibody to endotoxin, ketoconazole, simvastatin, and ibuprofen, have been tried and were largely found to be relatively ineffective and offered no survival benefit.[19,20] The current standard of care for the management of ARDS is largely supportive, with lung-protective ventilation and a fluid conservative strategy. The search for effective medicines to treat COVID-19 disease due to SARS-CoV2 infection-induced ARDS is of great interest. A variety of approaches to suppress the "cytokine storm" aiming to protect against lung damage, for example, by blocking individual inflammatory cytokines with anti-IL-1 or anti-IL-6 therapies are now being actively investigated. It is debatable, however, whether blockade of a single cytokine will be sufficient to suppress the "cytokine storm," which involves multiple cytokines and redundant systems maintaining the inflammatory response.

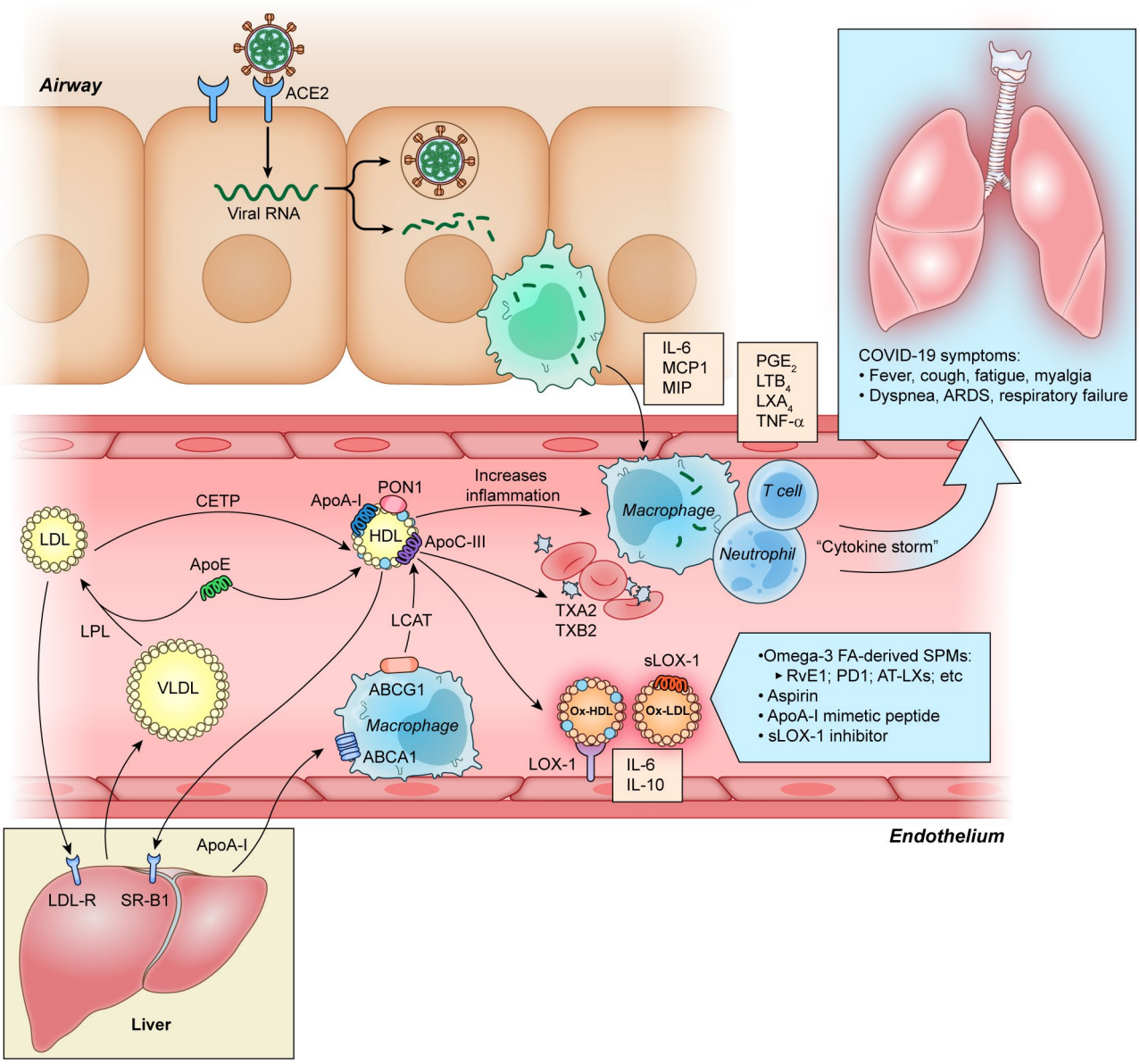

FIGURE 1 Proposed mechanism of COVID-19—associated dyslipidemia and impaired resolution of infection. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to angiotensin-converting enzyme 2 (ACE2) via spike protein, which facilitates entry into the cell with subsequent damage by alveolar macrophages. Subsequently, tissue microenvironment releases pro-inflammatory cytokines and chemokines (IL-6, MCP1, and MIP) promoting attraction of macrophages, neutrophils, and T cells. This cell activation leads to uncontrolled inflammation and immune dysregulation with further accumulation of eicosanoids like PGE_2, TXB_2, LTB_4, and LXA_4. Persistent inflammation culminates in the modulation of HDL-associated apolipoproteins, such as a decrease in apolipoprotein A-I (ApoA-I), ApoE, and an increase serum amyloid protein A, which adversely affects the anti-inflammatory, antioxidant, and immunomodulatory function of HDL. The imbalance in the antioxidant system also causes oxHDL modification via intracellular lectin-like oxLDL (LOX-1) receptor. The extracellular portion of LOX-1, serum-soluble form (sLOX-1), additionally stimulate interaction between oxidized lipids, and circulating macrophages resulting in pro-inflammatory cytokines release, such as IL-6, IL-10, and tumor necrosis factor-alpha (TNF-α). Impaired paraoxonase 1 (PON1) enzyme function on HDL, and excessive inflammatory response leads to further lipid oxidation. Excessive development of oxLDL and oxHDL results in lipoprotein transport alteration and impairment of the reverse-cholesterol transport (RCT) pathway (shown at left) characterized by insufficient ApoA-I interaction with the adenosine triphosphate-binding cassette transporter A1 (ABCA1) on macrophages and decreased cholesterol esterification by lecithin cholesterol acyltransferase (LCAT). This culminates in decreased return of cholesteryl esters to the liver either directly after interaction with hepatic scavenger receptor-B1 (SR-B1) receptors or indirectly after transfer to LDL by cholesteryl ester transfer protein (CETP) and uptake by hepatic LDL receptors (LDL-R). Low levels of ApoE and ApoC-III on HDL result in decreased lipoprotein lipase (LPL) activity, which in turn leads to VLDL and TGs accumulation

Here, we hypothesize that targeting immune-mediated inflammatory dyslipidemia in COVID-19, alone or in combination with other therapeutics, could possibly improve the clinical course in these patients.

2 | LIPOPROTEIN CHANGES IN COVID-19

The measurement of plasma lipids and lipoproteins is a critical part of the current approach to CVD risk management. Low HDL-cholesterol (HDL-C) is a strong predictor of CVD progression[21,22] and serves as a biomarker for increased risk of all-cause mortality and nonfatal myocardial infarction, even in statin-treated patients.[23] The best understood function of HDL is to promote reverse cholesterol transport (RCT) from the periphery to the liver, which can be assessed in clinical settings by measuring the first step in RCT, cholesterol efflux capacity (CEC).[24] In addition to its function in RCT, HDL particles have several other properties that may be relevant to modulation of the immune system and the control of infectious diseases. Specifically, among the several lipoproteins, HDL particles have the greatest affinity for binding and neutralization of pathogen-associated lipids (eg, lipopolysaccharide, lipoteichoic acid) that mediate the excessive immune activation in sepsis. HDL particles also have immunomodulatory, antithrombotic, and antioxidant effects.[25] For example, HDL-C levels have been shown to be inversely related to the frequency of several autoimmune diseases.[26]

High-density lipoprotein is a heterogeneous collection of particles with different sizes and apolipoprotein compositions. ApoA-I, the major protein constituent of HDL, is present in most HDL particles, whereas other apolipoproteins, such as ApoE, are associated with specific HDL particle subspecies. Cellular cholesterol efflux, the first step in RCT, is driven mainly by the interaction between relatively lipid-poor ApoA-I in small discoidal (pre-beta) forms of HDL and cell-bound transporters (ie, ABCA1, ABCG1, and SR-BI) (Figure 1).

High-density lipoprotein-associated apolipoproteins, such as apolipoprotein A-I (ApoA-I) and apolipoprotein M (ApoM), interact with lipid rafts on cellular membranes that are enriched in immune cell receptors, such as Toll-like receptors on macrophages[27] and T-cell receptors[28] and modulate the immune responses. Interestingly, previous and more recent literature suggest a causal inference for an inverse relationship between HDL-C, but not LDL-C or triglycerides, and risk of an infectious disease hospitalization.[29] Furthermore, the anti-inflammatory and antioxidant properties of HDL are significantly reduced during influenza[30] and HIV infection.[31]

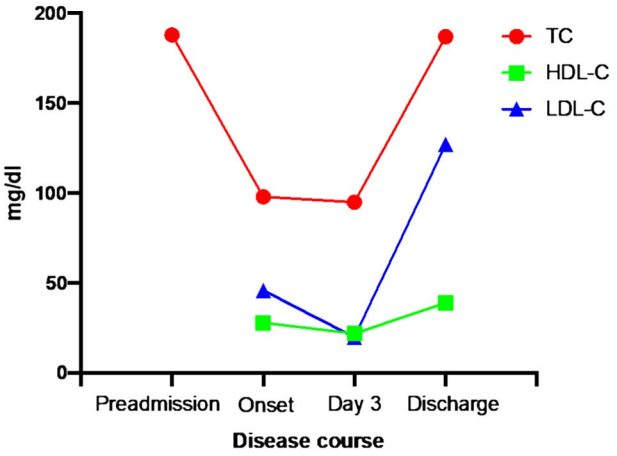

FIGURE 2 Lipid changes in COVID-19 patient over the course of disease

TABLE 1 The changes of laboratory data in a COVID-19 case

Parameters	Preadmission	Onset	Day 3	Day 60 (discharge)
White blood cells (/μL)	5600	6400	4600	7200
Neutrophils (/μL)	–	4845	3671	–
Lymphocytes (/μL)	–	909	400	–
Eosinophils (U/L)	–	6	55	–
Basophils (U/L)	–	64	23	–
Monocytes (U/L)	–	576	446	–
Lactate dehydrogenase (U/L)	232	354	370	174
Total cholesterol (mg/dL)	188	98	95	187
HDL cholesterol (mg/dL)	–	28	22	39
LDL cholesterol (mg/dL)	–	46	20	127
Triglycerides (mg/dL)	–	119	264	120
C-reactive protein (mg/dL)	0.1	13.1	21.0	0.0

Indeed, lower levels of both HDL-C and LDL-C were detected in HIV patients, with restored lipoprotein levels after treatment.[27] In the context of COVID-19, it has been recently reported that low levels of total cholesterol (TC), HDL-C and LDL-C are associated with disease severity and mortality.[32,33] Increased plasma triglyceride levels during infection and inflammation is also a well-known phenomenon.[29,34]

Illustrative of what has already been described in COVID-19,[32,33] we observed a similar trend of lipid changes in our clinical case of COVID-19 (Figure 2, Table 1). The patient was a 40-year-old male without a history of CVD and was not on any lipid-lowering treatment. After acute onset of COVID-19, the TC levels reduced by about half, accompanied by low HDL-C (22 mg/dL on Day 3) and low LDL-C (20 mg/dL at Day 3). The severity of the disease, including hypoxic pneumonia, reached its peak at Day 3. Changes in lipid levels appeared to parallel with increases in C-reactive protein (from 0.1 to 21.0 mg/dL at Day 3). These changes were accompanied by lymphocytopenia (from 909/μL onset to 400/μL at Day 3) and basopenia (from 64/μL onset to 23/μL at Day 3). Following treatment with an artificial respirator and supportive therapy, the patient's condition markedly improved, and TC returned to preadmission state at discharge (Day 60).

The mechanisms by which increased inflammation reduces HDL functionality are not clearly defined. It has been previously observed that inflammation alters HDL apolipoprotein composition. It has been described that inflammation alters hepatic apolipoprotein gene expression[35] and promotes binding of the pro-inflammatory serum amyloid protein A (SAA) which, in turn, displaces and decreases ApoA-I levels in HDL.[36] Moreover, in the setting of acute inflammation, decreased plasma levels of lecithin cholesterol acyltransferase (LCAT) may also alter HDL function and further deteriorate the inflammatory response.[37] Interestingly, it was recently reported that treatment of inflammation-altered HDL with LCAT ex-vivo reduces HDL-bound SAA, while increasing HDL-bound ApoA-I, and HDL function.[38] It was recently shown that SAA plasma levels are dynamically elevated with COVID-19 disease severity and SAA has been proposed as a biomarker for evaluating the severity and prognosis of COVID-19.[39] These findings suggest that HDL protein composition and function are altered in COVID-19 patients, raising the possibility that interventions, such as the LCAT treatment mentioned above, may improve HDL function and reduce disease burden.

Additional mechanisms leading to the dysfunction of HDL involve inflammation-induced oxidative modification of ApoA-I which reduces RCT.[40] An antioxidant enzyme present in HDL, paraoxonase 1 (PON1), is also inactivated under inflammation-induced oxidative stress,[41] which further compromises HDL function. In fact, low PON1 activity is associated with worse prognosis of CVD and was found to be decreased in various inflammatory[42] and infectious[43] diseases. Notably, the treatment of inflammation-altered HDL with LCAT ex-vivo, mentioned above, also significantly decreased HDL-bound PON1.[38] IL-10, which under certain circumstances may promote an inflammatory phenotype, can also decrease plasma HDL-C levels[44] by increasing micropinocytosis.[45]

Impaired HDL antioxidant activity further results in lipid oxidation, specifically generating oxidized LDL (oxLDL). As discussed further below, oxLDL and oxidized HDL (oxHDL) are potent activators of the oxidized LDL scavenge receptor (LOX-1), inducing further inflammation and aggravating tissue damage. Interventions to either improve HDL functionality, such as increasing LCAT activity mentioned above, or replenishment with functional HDL or relevant apolipoproteins, such as ApoA-I mimetic peptides may be effective in improving HDL functionality for the management of SARS-CoV-2 related complications.

3 | ApoE AND COVID-19

Besides ApoA-I, ApoE is also found on HDL, as well as ApoB-containing lipoproteins. ApoE serves as a ligand for the clearance of triglyceride-rich ApoB-containing lipoproteins by binding to membrane lipoprotein receptors in the LDL receptor family.[46-49] ApoE has many genetic variants affecting health and disease.[50,51] The most common isoform, ApoE3 has a Cys at codon 112 and Arg at codon 158. The ApoE2 isoform (Arg158Cys) is associated with decreased LDL-C but increased chylomicron and VLDL remnants, whereas the ApoE4 isoform (Cys112Arg) is associated with elevated plasma LDL-C and Alzheimer's disease.[46] Complete ApoE deficiency in humans results in increased plasma levels of triglycerides and cholesterol in ApoB-containing lipoproteins, decreased HDL-cholesterol, palmar-tuberoeruptive xanthoma, and premature cardiovascular disease.[52,53] It is well known that lack of ApoE in murine models also provokes atherogenesis accompanied by low HDL-C and high TG-rich lipoproteins.[54] Increases in both ApoE and phospholipid transfer protein (PLTP) activity have been shown to improve the delivery of energy substrates and phospholipids to tissues for sustaining cellular membrane homeostasis in intensive care patients.[55]

ApoE has additional functions beyond ApoB-lipoprotein uptake into cells. It has been shown to protect LDL from oxidation through its receptor-binding domain[56] and may also be involved in RCT.[57] ApoE-containing HDL particles promote cholesterol efflux from extrahepatic cells[58] by ABCA1- and ABCG1-dependent processes and this process is antagonized by the presence of ApoC-III.[59] ApoE is also expressed and secreted from monocytes and macrophages, with anti-atherosclerotic effects, and in other

tissues such as adipose tissue, brain, kidney and adrenal glands.[46,60] Interestingly, in the vascular endothelium, although endothelial cells do not produce ApoE, its local expression by macrophages has a paracrine effect on these cells, inhibiting VCAM-1, stimulating NO synthesis, suppressing endothelial activation, and decreasing adhesion of monocytes to the endothelium, whereas ApoE4 was found to antagonize these anti-inflammatory effects.[46]

Several findings suggest that deficits in ApoE function in SARS-CoV-2 dyslipidemia may contribute to disease progression and complications. Notably, ApoE is expressed in lung macrophages and also alveolar epithelial cells (both type I and type II).[61] ApoE-KO mice are highly susceptible to acute lung injury through an IL-6–dependent mechanism that increases endothelial cell permeability to oxLDL;[62] IL-6 is a major cytokine released during the COVID-19 cytokine storm.[63] In humans, ApoE can potentially function as an endogenous signal that primes the NLRPS inflammasome in alveolar macrophages from asthmatic subjects.[64] Moreover, the *APOE* gene is associated with modified lung physiology in humans.[65] The ApoE4 variant was also reported to predict COVID-19 severity. ApoE4/E4 homozygotes in the UK Biobank were more likely to test positive for COVID-19 (OR 2.31, CI 1.65 to 3.24, $P = 1.19 \times 10^6$). The association between ApoE4/E4 genotype and COVID19 was independent of pre-existing dementia, CVD or Type 2 diabetes.[61]

4 | OXIDIZED LIPOPROTEINS AND SCAVENGER RECEPTORS IN COVID-19

Low-density lipoprotein is the main vehicle for transporting cholesterol and phospholipids in the human circulation. During acute inflammation, LDL and its major apolipoprotein, apolipoprotein B (apoB) are oxidized (oxLDL). Lipid hydroperoxides derived from the lipoxygenase pathway,[66] and hydroxy fatty acids derived from arachidonic acid (AA) and linoleic acid (LA) accumulate and some are esterified into cholesterol esters, triacylglycerol, and phospholipids in oxLDL.[67] Oxidized phospholipids (OxPLs) in oxLDL are recognized as danger-associated molecular patterns (DAMPs) by cell scavenger receptors, inducing a cascade of intracellular signaling events, culminating in inflammasome activation and endothelial cell dysfunction, both of which contribute to atherosclerosis initiation and progression.[68] In addition, oxPL production is increased in the lungs of virus-infected humans and animals and oxPL induces macrophage cytokine production and acute lung inflammation in mice.[69]

The oxLDL scavenger receptor lectin-like oxLDL receptor (LOX-1), expressed in endothelial cells, macrophages, and smooth muscle cells, binds multiple ligands, including oxLDL, oxHDL, C-reactive protein, and advanced glycated end products.[70,71] oxLDL binding to LOX-1 results in oxLDL internalization and oxLDL cellular accumulation, which is thought to contribute to early atherosclerotic lesion development. In addition, ligand binding to LOX-1 triggers intracellular signaling processes leading to pro-apoptotic, pro-oxidant, and pro-inflammatory pathways, causing cell dysfunction associated with atherosclerosis and increased CVD risk.[70,72] Because of its binding and response to dysfunctional lipids, such as oxLDL and oxHDL, LOX-1 may be a key mediator of CVD by inducing inflammation-triggered atheroma growth and eventually plaque erosion and rupture.[73]

The serum-soluble form of LOX-1 (sLOX-1), the extracellular portion of LOX-1 produced by proteolytic shedding of the receptor, reflects membrane-bound intact receptor levels and is elevated in acute coronary syndrome (ACS),[74] stable coronary artery disease[75] and stroke.[76] The association of LOX-1 activation and acute inflammatory conditions raises the possibility that LOX-1 is also activated and may contribute to COVID-19 complications. In fact, recent clinical data suggest that SARS-CoV-2 may cause a pediatric multisystem inflammatory syndrome reminiscent of Kawasaki Disease (KD) in children.[77,78] Previous work has provided evidence for LOX-1 overactivation in KD patients.[79] These data, together with recent human pathology findings suggest that SARS-CoV-2 infection could trigger endothelial damage in multiple organs throughout the body.[80] Furthermore, LOX-1 blockade has been shown to protect mice from LPS-induced ALI,[81] suggesting that LOX-1 may play an important role in COVID-19 complications and is another potential target for therapy.

5 | SPECIALIZED PRORESOLVING MEDIATORS IN COVID-19

The continuous inflammatory response driven by the "cytokine storm," which includes release of the pro-inflammatory cytokines (TNF-α, IL-6, IL-8, and IL-10)[82] and lymphopenia, are considered to be one of the main cause of life-threatening complications in SARS-CoV-2 patients. The immunological phenotype characterizing COVID-19 highlights the importance of T lymphocytes, with decreased numbers of circulating CD4+/CD8+ T cells in particular.[83] However, the direct effect of the released cytokines and chemokines results in massive cell death that provokes a cascade of biological reactions, including production of macrophage-derived eicosanoids that further potentiate inflammation.[84]

Until recently, inflammation resolution, the process by which an inflamed system returns to homeostasis and reduces inflammation, was thought to be a passive process relying mainly in the biological "decay" of pro-inflammatory factors. It is now known, however, that inflammation resolution

is, in fact, an active process mediated by specific molecules collectively referred to as specialized proresolving mediators (SPMs).[85]

Omega-3 polyunsaturated fatty acids (PUFAs), which are transported in plasma on lipoproteins, serve as precursors to SPMs production by macrophages and neutrophils and treatment with PUFAs increase SPM levels in circulation.[86] The main omega-3–derived SPMs include lipid mediators called E-series resolvins from eicosapentaenoic acid (EPA) and D-series resolvins, protectins and maresins from docosahexaenoic acid (DHA). A key mechanism of action of SPMs to suppress inflammation is the induction of efferocytosis, the process by which macrophages and other phagocytotic cells engulf and eliminate apoptotic cells. For example, it was shown recently that the EPA-derived resolvin E1 (RvE1) promotes phagocytosis of apoptotic neutrophils and reduces acute lung inflammation in a murine model.[87] Moreover, the DHA-derived protectin D1 (PD1), is an innate suppressor of influenza virus replication.[88] There are numerous studies now showing divergent properties for EPA and DHA in modulating inflammation. For example, EPA is considered to be a more potent inhibitor than DHA of the inflammatory response in human asthmatic alveolar macrophages[89] and is more efficient in reducing AA products.[90] In contrast, endogenous PD1 has been described as a pivotal counterregulatory signal in allergic airway inflammation[41] with overall DHA derivatives reported to be biologically more stable as compared to SPMs from EPA and AA.[91] In addition, EPA-rich fish oil increased ApoM abundance in plasma and HDL versus DHA-rich fish oil supplement.[92]

TABLE 2 Adjunctive therapies currently under investigation for COVID-19

Therapy	Identifiers ClinicalTrials.gov/ ChiCTR.org.cn/ clinicaltrialsregister.eu (EudraCT)	Mechanism of action
NSAID		COX-1 and COX-2 inhibitor
Aspirin (acetylsalicylic acid)	NCT04365309	
+ Losartan + Simvastatin	NCT04343001	
+ Vitamin D	NCT04363840	
Naproxen	2020-001301-23	
Corticosteroids	NCT04273321	Multifactorial
	NCT04323592	
Statin		HMG-CoA reductase inhibitor
Ulinastatin	CHICTR2000030779	
Ulinastatin	CHICTR2000032135	
Atorvastatin	NCT04380402	
Omega-3 PUFAs		Multifactorial
EPA	NCT04335032	
EPA + gamma-linolenic acid and antioxidants	NCT04323228	
Sitagliptin	NCT04365517	Dipeptidyl peptidase-4 (DPP-4) inhibitor
Colchicine	NCT04355143	Inhibition of microtubule polymerization
	NCT04322565	
	NCT04326790	
	NCT04363437	
	NCT04375202	
	NCT04350320	
	NCT04367168	
	NCT04328480	
	NCT04360980	
	NCT04322682	
	2020-001603-16	

Recently it has been found that ApoE-KO mice consuming an omega-3 fatty acid-deficient diet have significant accumulation of pro-inflammatory eicosanoids in lungs.[93] Supplementing the diet with omega-3 fatty acids reduced accumulation of these pro-inflammatory eicosanoids and, interestingly, supplementation with omega-3 fatty acids and aspirin significantly reduced these mediators even further. Moreover, combining the omega-3 fatty acid diet with aspirin led to greater abundance of the main EPA- and DHA-derived pathway metabolites, anti-inflammatory 18-hydroxyeicosapentaenoic acid (18-HEPE), and 17- hydroxydocosahexaenoic acid (17-HDHA).[84] In addition to respiratory symptoms, abnormal coagulation with thromboembolic disease is considered to be a significant factor in COVID-19 deterioration and clinical outcomes.[94] Indeed, ApoE-deficient mice showed evident endothelial dysfunction, which along with high ACE2 receptor expression and TxB_2 accumulation can lead to excessive vascular permeability and increased blood coagulation. It should also be mentioned that endothelial cells represent a significant proportion of lung cells.[95] Of interest, omega-3 fatty acid supplementation and aspirin treatment significantly suppressed lung TxB_2 levels in ApoE-KO mice.[93]

Taking together, these observations suggest that direct treatment with either EPA- or DHA-derived SPMs in the course of COVID-19 might have potential therapeutic effect.[96,97] In fact, omega-3 fatty acids are currently being tested in several ongoing clinical trials using EPA monotherapy or as a supplement mixture containing EPA, gamma-linolenic acid, and antioxidants in COVID-19 patients (Table 2).

6 | CONCLUSIONS

The "cytokine storm" underlying COVID-19 produces immune-mediated inflammatory dyslipoproteinemia, leading to low HDL-C and LDL-C levels, elevated triglycerides, increased lipoprotein oxidation, low ApoE levels, and impaired inflammation resolution due to decreased SPMs biosynthesis. These lipid abnormalities might be modified by pharmacological agents that increase ApoA-I and HDL plasma levels. For example, ApoA-I mimetic peptides are known to inhibit inflammation induced by influenza infection in a model of human pneumocytes[98] and modulate the severity of neutrophilic airway inflammation in a mouse asthma model.[99] Raising HDL may also restore lipid transport function, along with improving the antioxidant properties of HDL.[59] We also propose that low levels of ApoA-I and ApoE might be in part responsible for distinct lung inflammation, as shown previously in ApoE-deficient mice and available but limited human data.

Other HDL-raising pharmacological compounds that could be considered as adjunctive therapy for COVID-19, include fibrates, CETP-inhibitors, recombinant LCAT,[38] and small molecules that upregulate ApoA-I production.[100] Increasing HDL would have the added benefit of decreasing platelet hyperreactivity by limiting intraplatelet cholesterol overload, along with suppressing the coagulation cascade and inhibiting platelet activation.[101]

The rise in eicosanoids and hypercoagulation that occurs in COVID-19 may possibly controlled by combined therapy with omega-3 fatty acids and aspirin, which by itself has anticoagulant properties. This drug combination has been clinically validated and presents with low risk of interactions with other COVID-19 treatments. Omega-3 fatty acids in combination with aspirin might represent a valuable alternative treatment by producing proresolving aspirin-triggered lipoxins (AT-LXs) and decreasing eicosanoids such as PGE_2 and TxB_2.[102] Treatment with SPMs themselves, such as E- and D-series resolvins, may also be effective in patients with severe COVID-19, due to their effective tissue availability and fast biological action.[96]

Any pharmacological agent added for the treatment of COVID-19 will require, however, close monitoring for possible drug interactions or any other unanticipated consequences.[103] This requires the need to perform randomized placebo control clinical trials for ultimately establishing the safety and efficacy of any new drug added to the treatment of COVID-19.

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CONFLICT OF INTEREST

The author declares no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

A.V. Sorokin conceived and researched the hypothesis proposed in this manuscript and wrote the manuscript. A.T. Remaley, S.T. Karathanasis, Z.-H. Yang, L. Freeman, and K. Kotani critically reviewed the manuscript and contributed to the hypothesis exploration. K. Kotani analyzed clinical case data.

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