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Alterations of Lipid Profile in COVID-19: A Narrative Review

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Abstract: The COVID-19 pandemic has led to over 100 million infections and over 3 million deaths worldwide. Understanding its pathogenesis is crucial to guide prognostic and therapeutic implications. Viral infections are known to alter the lipid profile and metabolism of their host cells, similar to the case with MERS and SARS-CoV-2002. Since lipids play various metabolic roles, studying lipid profile alterations in COVID-19 is an inevitable step as an attempt to achieve better therapeutic strategies, as well as a potential prognostic factor in the course of this disease. Several studies have reported changes in lipid profile associated with COVID-19. The most frequently reported changes are a decline in serum cholesterol and ApoA1 levels and elevated triglycerides. The hyper-inflammatory state mediated by the Cytokine storm disturbs several fundamental lipid biosynthesis pathways. Virus replication is a process that drastically changes the host cell's lipid metabolism program and overuses cell lipid resources. Lower HDL-C and ApoA1 levels are associated with higher severity and mortality rates and with higher levels of inflammatory markers. Studies suggest that arachidonic acid omega-3 derivatives might help modulate hyper-inflammation

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and cytokine storm resulting from pulmonary involvement. Also, statins have been shown to be beneficial when administered after COVID-19 diagnosis via unclear mechanisms probably associated with anti-inflammatory effects and HDL-C rising effects. (Curr Probl Cardiol 2022;47:100907.)

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, is an enveloped, positive-sense, single-stranded RNA virus from the family Coronaviridae. It is a member of Nidovirales, the order known to cause respiratory and GI infections ranging in severity from a mild common cold to illnesses as severe as MERS and SARS.[1]

Lipids play different metabolic roles as structural components, energy resources, signaling mediators, as well as roles in infections, and viral infections in particular.[2-4] Many macrophage regulation and immune-modulatory pathways depend on lipids,[5] and the role of lipid metabolism in pulmonary infections and inflammatory states have been observed.[6] The effect of Coronaviruses on lipid metabolism and serum lipid profile items had been observed before the current pandemic. Several studies have reported important changes in the lipid profile of patients with COVID-19 infection.[4,5,7-11]

In this article, we initially review how the lipid profile changes in COVID-19 and its prognostic role by assessing its relationship with disease severity. Then, we examine the ways SARS-COV2 infection causes these changes by studying the underlying cellular and molecular mechanisms. Finally, we study the potential therapeutic agents targeting these mechanisms by providing evidence on fish oil and statins.

Lipid Profile Changes in COVID-19

Lipid profile changes have been reported since the early stages of COVID-19 pandemic; most notably as decreases in cholesterol levels.[12] Qin et al found decreased levels of total cholesterol (TC) and LDL-C in a retrospective study on the lipid profiles of 248 COVID-19 patients.[13] These measures were negatively correlated with the patients' length of hospital stay. Also, the patients had lower TC and LDL-C levels upon admission that would gradually recover as the patients' clinical condition improved.[13,14] Another retrospective study on 102 patients in Mexico

suggested that low levels of TC and LDL-C could predict more severe involvement.[9] They also reported high TG levels as well as high VLDL-C levels. A study in Saudi Arabia on 80 COVID-19 patients reported an increased risk of cardiovascular diseases due to changes in the patients' lipid profiles: decreased level of TC (both HDL-C and LDL-C) and increased TG.[8]

A comprehensive study on serum lipids at cellular levels reported altered cholesterol metabolism resulting from COVID-19 as responsible for the depressed level of circulating cholesterol.[11] They postulate that infection with SARS-COV-2 reduces Apo-A1 and HDL-C levels, both of which relate to the severity of the disease. They also reported that serum lipidome in COVID-19 patients highly resembled the membranes of a certain type of membrane-bound extracellular vesicles, rich in GM-3 (monosialodihexosylganglioside) and Sphingomyelins (SM). In a series of 46 COVID-19 patients, a reduction in 100 lipids was noticed, most notably in the Apolipoproteins related to macrophage regulatory processes.[5] ApoA, sphingolipids, Glycerophospholipids, some steroid precursors (e.g. 21-hydroxypregnenolone), ApoM, and choline were down-regulated, the two latter of which were seen in severe involvement. Choline, a precursor of phosphocholine, is a molecule essential in *de novo* biosynthesis of phosphatidylcholine – the main phospholipid in cell membranes.[15] They suggest that the decrease in choline levels might be due to increased macrophage activation and activity.[5,11]

To summarize, the alteration observed by most studies in COVID-19 patients' lipid profiles has been a reduction in cholesterol and apolipoprotein levels and increased TG.

Lipid Alterations Associated With COVID-19 Severity

According to plasma content studies, levels of lipid alteration and the severity of the infection are correlated and many research projects have found an association between COVID-19 and lipid biomarkers.[14] A cross-sectional analysis of 1411 hospitalized patients with COVID-19 showed that low HDL-C and high TG before infection and upon admission were strong predictors of disease severity and correlated with higher D-dimer and ferritin levels.[16] Another large study showed that while TC and LDL-C were lower among all patients with COVID-19 and LDL-C declined as the disease progressed, importantly HDL-C was only abnormally lower in critical cases.[17] Another study on 228 COVID-19 cases from China showed that LDL-C, HDL-C, and TC were lower among these patients compared to healthy controls and that lower HDL-C upon

admission was a negative prognostic factor for negative disease outcomes.[18,19] A study of lipid profile trends in ICU-admitted COVID-19 patients showed that all patients had low LDL-C and HDL-C levels; Although this issue was not a predictor of mortality, lower cholesterol levels at the start of ventilator-associated pneumonia were associated with increased mortality.[20]

Two prospective studies to assess lipid alterations in COVID-19 found that HDL-C and Apo-A1 are inversely related to disease severity measures such as mortality rate and inflammatory markers such as CRP and IL-6.[5,21] They also reported significantly higher TG levels and lower TC and LDL-C levels in their severe patients compared to milder cases.[11] Many studies similarly showed an inverse relationship between LDL and HDL with C-reactive protein (CRP) as a marker of severity of inflammation.[14,16,18]

Fan et al. compared 17 patients who survived COVID-19 with 4 patients who died of the disease and found that although LDL-levels were decreased in both groups, the lipid dysregulation was more persistent, severe, and progressive among non-survivors while it took a course through recovery in patients who survived the infection.[19]

Mechanisms of Alterations in Lipids

The role of lipids in biology, like backbones of the cell membrane, in cellular interconnection, membrane trafficking, energy resources, and heat insulation is well-known. They are also essential for viruses to cross the host cell membrane. Besides, it is known that viral infections alter lipid metabolism in favor of virus replication.[2] Lipidomic studies have revealed that coronavirus significantly modifies the lipid composition of infected cells.[22] Viruses employ and modify both lipid signaling and metabolism to benefit their replication as lipids constitute not only the main structure of membranes but also play important roles as intercellular signaling agents and energy sources.[23] Replication of enveloped viruses like SARS-CoV-2- which enter the cells via endocytosis and use intracellular organelles to produce their different parts requires lipid resources.[25] Therefore, studying how an infection with SARS-COV-2 affects lipid metabolism and profile, might shed light on the correlation between lipid profile and inflammatory processes during COVID-19.

Direct Intracellular Changes of Lipid Metabolism

Lipids are of essential importance in viral infection: they provide structural and energy resources to create membranes for cells and viral

organelles.[26,27] RNA-viruses target lipid synthesis to modulate inter and intracellular signaling in favor of their needed processes in creating their required particles for host cell entry, infectivity, and hiding from the immune system.[19]

Lipid rafts are dynamic regions in the cell membrane with a size ranging from 10 to 200 nm that include sphingolipids, glycosphingolipids, cholesterol, and GPI-linked proteins, specialized particles that participate in various mechanisms such as intercellular signaling, trafficking, polarity regulation endocytosis, and autophagy.[5,27] To enter the host cells, SARS-CoV-2 binds to ACE2 receptors, found inside cell membrane lipid rafts, to produce transformations in the viral molecules and initiate a signaling cascade that allows for virus endocytosis.[28,29,26]

Like other positive-sense RNA viruses, SARS-COV2 modifies host cell membranes to create viral replication organelles (RO); factories for RNA synthesis and viral replication.[24] Electron microscopy has shown that SARS-COV-2 produces types of double-layered structures called double-membrane vesicles (DMV)s, consisting of a plasma membrane interspace with various organelles.[23,25,26] SARS-COV-2 exploits endosomes as replication organelles.[23] The replication of SARS-COV-2 is a heavy burden on the host cells' endoplasmic reticulum (ER), so much that the ER fails to maintain its homeostasis and produces misfolded proteins. This initiates the unfolded protein response (UPR) pathway through which apoptosis is preferred over further attempts to restore ER and intracellular homeostasis.[27,28] UPR activation, through a chain of reactions, stimulates sterol regulatory-element binding protein-1 (SREBP-1) which transcribes genes involved in the down-regulation of lipids namely fatty acid synthase (FASN), Acetyl-CoA carboxylase (ACC), and stearoyl-CoA desaturase-1 (SCD1).[29] This provides the virus with the required structural lipids to create organelles for replication. Increased lipid stocks also expand DMV luminal volumes decreasing the effective concentration of misfolded virus proteins which in turn prevents apoptosis induced by UPR in favor of the virus.[30]

During its replication phase, SARSCOV2 targets lipid droplets: lipid-rich cellular organelles that store cholesterol esters and triacylglycerols for various purposes.[31,32] Pharmacological inhibition of LD formation suppresses SARS-CoV2 replication, production of inflammatory mediators, and cell death.[33]

Apolipoproteins

Several COVID-19 studies have reported changes in apolipoprotein levels along with other changes.[5,21] For instance, a relationship between

ApoE and COVID-19 severity might be due to neighboring genes in the gene cluster that happens in response to inflammation.[34] Another example of this is the rise in lipoprotein Lp A that is suggested to be a response to increased IL-6 levels; Lp A has a receptor for IL-6 and thus is increased during cytokine storm as an acute phase reactant.[35]

Adiponectin

Adiponectin is a protein hormone closely related to T2DM pathogenesis.[36] Plasma adiponectin levels were found to predict and improve insulin sensitivity[36] and can thus benefit lipid metabolism. On the one hand, adiposity, insulin resistance, and obesity were shown to be related to low adiponectin levels; On the other hand, higher adiponectin concentrations benefit individuals independent of existing obesity.[36] Since insulin is involved with lipid metabolism, targeting adiponectin levels can be a strategy to improve HDL-C levels in patients, as Messina et al. suggest through an appropriate diet.[37] They suggest that holding a healthy diet to maintain adequate levels of adiponectin is both good for prevention of and recovery from an infection. Also, the correlation between higher adiponectin and higher HDL-C levels is independent of insulin sensitivity of glucose and can directly lower free fatty acids in circulation.

Cytokine Storm

De Lorenzo suggests that the cytokine storm that occurs as a result of COVID-19, is key to various pathologies of this disease, including endothelial dysfunction. Lipid metabolism can be altered directly by the cytokine storm and indirectly by the effect of endothelial dysfunction. Many studies have reported that inCOVID-19 is associated with an exaggerated immune response that results in excessive production of various pro-inflammatory cytokines and cells referred to as "cytokine storm".[38,39] Cytokines are proteins serving as mediators to help initiate and control pro- and anti-inflammatory immune processes.[40] This syndrome, expected to occur within the second week from the onset of symptoms and particularly in critically ill COVID-19 patients suffering pulmonary involvement,[39,41,42] can seriously complicate the patient's condition by causing a systemic inflammatory state resulting in multiple organ failure.[39] De Lorenzo et al. noted that endothelial dysfunction is a remarkable component of COVID-19 pathogenesis which also plays an important role in cardiovascular complications.[43,44] A healthy endothelium is essential to keep vascular homeostasis, including blood pressure, insulin resistance, lipids circulation, and particularly expressing ACEII

receptors – a means for the novel coronavirus to infer infectivity.[22] The excess production of inflammatory agents increases vascular permeability, allowing more inflammatory cytokines and cells into the healthy tissues, which in turn expand the inflammation further and can account for symptom exacerbation in the inflammatory phase of the infection.[10]

Therapeutic Implications

Polyunsaturated Fatty Acids

The important role of Arachidonic acid both in producing cytokines (causing a cytokine storm) and in resolving inflammation has been extensively described.[44-46] PUFAs are Arachidonic acid derivatives that act both as inflammatory and inflammation-resolving agents.[40]

Studies show that the resolution of the inflammatory phase in COVID-19 does not occur passively by consumption of inflammatory mediators, but is rather an active process that can be switched on.[47,48] Omega-3 long-chain fatty acids have been associated with inflammation resolution, reduced severity of lung involvement, and lower infection severity in humans as well as animal models.[49-53] The most important precursors of omega-3-long-chain-poly-unsaturated-fatty-acids (ω-3-LC-PUFA)s are α-linolenic acid (ALA), and long-chain derivatives such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[39] PUFAs modulate and regulate membrane domain properties. Since the lipid raft microdomains (discussed earlier) are important mediators in virus entry, this "lipid raft-regulating" effect might be a therapeutic strategy since it will interfere with the mechanisms by which SARS-COV-2 exploits cell lipid metabolism. Among ω-3-LC-PUFAs, DHA has been shown to directly modulate lipid rafts.[54] PUFAs interfere with virus-induced lipid metabolism to restore homeostasis by inhibiting the cell's lipid biosynthesis apparatus. EPA and DHA inhibit the transcription and maturation of SREBP to its mature active form and in turn, weaken the replication processes via decreased lipid biosynthesis.[55] Furthermore, DHA and EPA can down-regulate the transcription of ACC, FASN, and Stearoyl-CoA desaturase further slowing down lipid production.[55]

Administering ω-3-LC-PUFAs in hospitalized COVID-19 patients lowered the incidence of superinfections and sepsis to 40% and 56% respectively.[56] It also correlated with shorter ICU stay, decreased mortality rate, shorter hospital stay, and lower need for mechanical ventilation.[57-60]

Omega 3 PUFAs are well-known specialized agents that initiate and take part to start resolving the inflammation[61]. Specialized pro-resolving lipid mediators (SPMs) work differently from Anti-inflammatory medications; rather than ceasing the inflammatory processes, they switch the cells towards resolving the inflammation. Three important SPM types are resolvins, maresins, and protectins. They reduce inflammation via various mechanisms; including destabilizing lipid rafts, decreasing vascular permeability, reducing immune cell recruitment, inhibiting the inflammatory activities of polymorphonuclear white blood cells, turning macrophages towards an anti-inflammatory type, stimulating neutrophil phagocytosis,[62,63] and down-regulation of pro-inflammatory cytokines by inhibiting NF-kB pathway.[64] They also stimulate wound healing and induce tissue regeneration.[65] The biosynthesis of SPMs highly depends on PUFAs, most importantly on DHA and ETA.[40]

Statins

Statins may be another plausible therapeutic adjunct in COVID-19 management owing both to their anti-inflammatory as well as HDL-enhancing effects.[66-68] These drugs have been mainly used for their LDL-lowering effects but research shows they also have TG-lowering and HDL-raising effects independent of LDL-reduction. The HDL-raising effect is stronger among patients with lower baseline HDL-C, higher baseline TG, levels. It is important to note that certain statins may have stronger HDL-raising capacities than others: Rosuvastatin and Simvastatin being superior to Atorvastatin, the magnitude of their effect increased in a dose-response manner.[69] However, there has been a concern for these agents potentially aggravating SARS-COV2 replication by enhancing cellular entry via inducing the ACE-2 gene.[70] At least two systematic reviews have specifically addressed the effects of statins among patients with COVID-19. One systematic review that included 13 RCTs with a total of 52,122 patients showed that while prehospital use of statins did not affect the rate of mortality, its prescription during hospital admission significantly reduced the risk of death (RR=0.54 (95%CI:0.5-0.58)[66]. The result of another systematic review that included 13 cohorts with over 110,000 patients had consistent results with a death-hazard ratio of 0.53 (95%CI: 0.26-1.64) among patients who had administered statins after a COVID-19 diagnosis.[71] Both of these studies provide supportive evidence for the benefit of statins in COVID-19.

Conclusion

Lipid metabolism is altered in patients with COVID-19 through direct cellular infection as well as systemic inflammatory response. These alterations

mainly result in a decrease in TC, LDL-C, and HDL-C levels and increased TG levels among these patients. Lower HDL-C levels appear to have a significant prognostic role in predicting poor clinical outcomes. Certain interventions such as fish oil and statins targetting this aspect of COVID-19 pathogenesis may have beneficial roles for these patients.

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