Lipids in SARS-CoV-2 Infection

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Being major components of cellular and viral membranes, lipids are undoubtedly involved in viral infections. Membrane/lipid rafts, i.e., cholesterol-rich subdomains of plasma membranes, are crucial elements for membrane fusion and endocytosis.

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1. Introduction

SARS-CoV-2 is a novel coronavirus, and one responsible for the COVID-19 pandemic. The first official reports from Wuhan City, China about numerous cases of acute, severe respiratory syndrome appeared in December 2019, and the coronavirus itself was isolated in January 2020. The rapid spread of the coronavirus around the world forced the WHO to declare a pandemic on 11 March 2020 [1].

Infection with new coronavirus is particularly dangerous for the elderly and for people with cardiovascular disease, obesity, diabetes, chronic respiratory disease, cancer, or decreased immunity [2]. The presence of such comorbidities requires the use of different drugs, and these can affect the response to viral infections in a number of ways. A good example is the use of statins, which are commonly prescribed for high-risk patients worldwide because of their beneficial effect on cardiovascular events [3].

Recent studies indicate that the use of statins lowered mortality by 42% in hospitalized patients with COVID-19 (aHR = 0.58 with (0.43–0.8) 95% CI; p = 0.01); they were also associated with a 20% lower risk of *acute respiratory distress syndrome* (ARDS) (IRR = 0.80 with (0.67–0.96) 95% CI; p = 0.016) and 49% lower risk of mechanical ventilation (aHR = 0.51 with (0.34–0.78) 95% CI; p = 0.02). Interestingly, statin users were significantly older (66.0 vs. 57.0 years of age, p < 0.001), and were more likely to demonstrate comorbidities including hypertension (81.5% vs. 30.3% p < 0.001), diabetes (34.0% vs. 14.6% p < 0.001), coronary heart disease (36.3% vs. 5.7% p < 0.001), cerebrovascular disease (8.8% vs. 2.3% p < 0.001) compared to non-users [4]. A meta-analysis by Kow et al. including 8990 COVID-19 patients found statins reduce the risk of fatal or severe disease by 30% [5]. It should be emphasized that most of the studies concerned the chronic use of statins prior to SARS-CoV-2 infection—there is still insufficient evidence of the benefits of initiating such therapy *de novo* in COVID-19.

These results may be caused by the pleiotropic activity of statins, and recent studies suggest various mechanisms that may directly affect SARS-CoV-2 endocytosis (ACE2), replication (main protease and RNA polymerase) or indirect mechanisms unrelated to coronavirus infection, such as e.g., anti-inflammatory, anti-coagulant effects or endothelial function improvement [6][7][8][9][10][11]. In addition, it is very likely that the direct effect on the ACE2 receptor could be of particular importance for the new British coronavirus strain, possibly due to the stronger interaction between the spike protein and the ACE2 receptor [12].

Despite the benefits of this therapy, statin use is associated with a number of side effects, including myopathies, elevated hepatic enzymes and increased risk of diabetes. In addition, some comorbidities of COVID-19 patients, such as nephropathy, diabetes or multiorgan failure, may also affect the efficiency and safety of this therapy [13]. However, Xiao-Jying et al. report that statin use in hospitalised COVID-19 patients was not associated with the increase of creatinine kinase (CK > upper limit of normal ULN aHR 0.97 (0.8–1.17) p = 0.715) or alanine transaminase (ALT > 3ULN aHR 0.98 (0.76–1.26) p = 0.852) [4].

2. Lipids in SARS-CoV-2 Infection

Being major components of cellular and viral membranes, lipids are undoubtedly involved in viral infections. Membrane/lipid rafts, i.e., cholesterol-rich subdomains of plasma membranes, are crucial elements for membrane fusion and endocytosis. An in vitro study found ApoE-mediated cholesterol influx to cause ACE2 translocation to lipid rafts, and

depletion of cholesterol with methyl-beta-cyclodextrin (MβCD) reduced the ACE2 receptor localization with lipid rafts by 70% [14]. Lipids not only facilitate membrane fusion, enabling viral cell entry, but also play crucial roles in viral envelopment, replication and exit, i.e., the further steps of viral invasion [15]. Viruses are able to alter the host lipid metabolism to produce fatty acids for their own use; in previous studies, inhibition of fatty acid synthesis was associated with a significant decrease in viral replication [16]. In addition, cholesterol depletion by pretreatment of Vero E6 cells with MβCD was found to cause a significant decrease in the production of SARS-COV-1 particles by infected cells in vitro; this effect was reversed after cholesterol was added to the cellular medium, indicating that the observed reduction of virus particle release was caused by the loss of cholesterol in the cell membrane [17]. Extracting cholesterol from human embryonic kidney 293T cell membranes with MβCD reduced the entry of retroviruses pseudotyped with the SARS-CoV-2 S proteins (SARS2-PV) by 90% [14].

In addition, metabolomic studies suggest that lipids are strongly associated with the host response to SARS-COV-2 infection. Barberis et al. report that the severity of the disease was characterized by the activation of gluconeogenesis and the metabolism of porphyrins, which play a crucial role in the progress of the infection. Down-regulation of glycerophospholipids and upregulation of lysophospholipids, arachidonic and oleic acids was observed in sera of COVID-19 patients, indicating that phospholipase A2 (PLA2) is involved in COVID-19 pathogenesis and progression [18]. The activity of PLA2 stimulates the increase of inflammatory lipid mediators such as prostaglandins, leukotrienes and lysophospholipids; these may also play a crucial role in the regulation of inflammatory response, which can influence the prognosis of COVID-19 patients [19]. Moreover, the inhibition of cytosolic phospholipase A2 (cPLA2) with the use of the low-molecular-weight nonpeptidic inhibitor pyrrolidine-2 (Py-2) blocked the replication of *Coronaviridae* viruses [20].

Patients with SARS-COV 2 infection experience serum lipid disturbances. Studies have found TC, LDL-C and HDL-C levels to be significantly lower in COVID-19 patients than in uninfected patients. Lipid levels were also correlated with the COVID-19 severity. Patients with median total cholesterol 173 mg/dL (148, 204) tended to demonstrate a mild COVID course, those with 167 mg/dL (138, 197) demonstrated a severe course, while those with 125 mg/dL (95, 162) demonstrated a critical course ($p < 0.05$). Similarly, for LDL-C, median 91 mg/dL (76, 104) was associated with a mild COVID course, 86 mg/dL (69, 102) with a severe course and 69 mg/dL (48, 81) with a critical course ($p < 0.02$). For HDL-C, median 50 mg/dL (42, 59) was associated with a mild course, 50 mg/dL (41, 59) with a severe course and 36 mg/dL (29, 43) with a critical course ($p < 0.05$). For triglicerides, median 150 mg/dL (124, 213) was associated with a mild COVID course, 142 mg/dL (89, 189) with a severe course and 115 mg/dL (88, 186) with a critical course ($p < 0.01$) [21][22].

Low HDL was suggested to be an independent risk factor for a severe course of COVID-19. COVID-19 patients with low HDL at admission (median, 27 vs. 31 mg/dL, $p = 0.032$) had nearly a three-fold greater risk of developing a severe course of the disease than those with high HDL-C (HR 2.827, 95% CI 1.190–6.714, $p = 0.019$). This may be helpful in identifying patients at high risk of critical COVID-19 course who need more intense monitoring [23]. Unfortunately, the authors did not consider lipid lowering therapy in their analyses; however, these studies were performed on a Chinese population, where the use of statins is not common, even in secondary prevention [24].

Association of COVID-19 course and hypolipidemia may be supported by the fact, that SARS-CoV-2 requires lipids for the infection. There is no evidence that statins by lowering lipids may exacerbate COVID-19. On the contrary, in retrospective analysis of 170 hospitalized COVID-19 patients the use of statins prior to admission was associated with reduced risk of severe course of the disease by 70% (adjusted OR 0.29, 95%CI 0.11 to 0.71, $p < 0.01$) [25]. Statins, as hypolipidemic drugs may decrease the infectivity of SARS-CoV-2 by disrupting lipid rafts and lowering membrane cholesterol levels [26]. However statins are not only associated with lowering lipid levels, they also exert pleiotropic effects such as attenuating inflammation and atherosclerotic plaque stabilization which may be crucial in patients with atherosclerosis and COVID-19 [27]. The issue of atherosclerotic plaque stability should be more investigated in patients with SARS-CoV-2 infection.

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