MINI-REVIEW | Immunometabolic Cross-Talk and Regulation of Endocrine and Metabolic Functions

Cholesterol: A new game player accelerating vasculopathy caused by SARS-CoV-2?

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Submitted 26 May 2020; accepted in final form 3 June 2020

Cao X, Yin R, Albrecht H, Fan D, Tan W. Cholesterol: A new game player accelerating vasculopathy caused by SARS-CoV-2? Am J Physiol Endocrinol Metab 319: E197–E202, 2020. First published June 5, 2020; doi:10.1152/ajpendo.00255.2020.—The pandemic of coronavirus disease (COVID-19) has become a global threat to public health. Functional impairments in multiple organs have been reported in COVID-19, including lungs, heart, kidney, liver, brain, and vascular system. Patients with metabolic-associated preconditions, such as hypertension, obesity, and diabetes, are susceptible to experiencing severe symptoms. The recent emerging evidence of coagulation disorders in COVID-19 suggests that vasculopathy appears to be an independent risk factor promoting disease severity and mortality of affected patients. We recently found that the decreased levels of low-density lipoprotein cholesterols (LDL-c) correlate with disease severity in COVID-19 patients, indicating pathological interactions between dyslipidemia and vasculopathy in patients with COVID-19. However, this clinical manifestation has been unintentionally underestimated by physicians and scientific communities. As metabolic-associated morbidities are generally accompanied with endothelial cell (EC) dysfunctions, these pre-existing conditions may make ECs more vulnerable to SARS-CoV-2 attack. In this mini-review, we summarize the metabolic and vascular manifestations of COVID-19 with an emphasis on the association between changes in LDL-c levels and the development of severe symptoms as well as the pathophysiologic mechanisms underlying the synergistic effect of LDL-c and SARS-CoV-2 on EC injuries and vasculopathy.

COVID-19; endothelial cells; hypertension; LDL; obesity; SARS-CoV-2; thrombosis; vasculopathy

INTRODUCTION

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (15), which was first reported in December 2019 from Wuhan, China (18). As of May 25, 2020, more than 5.4 million infections and 345,000 deaths have been reported in 188 countries and regions. The United States alone has registered more than 1.6 million cases and 97,000 deaths (20a). Scientists are just beginning to understand the nature of the harm caused by this disease. Patients with metabolic-associated preconditions are susceptible to experience more severe symptoms. Dyslipidemia leads to dysfunction of blood vessels in various cellular activities and is intrinsically associated with these metabolic and vascular comorbidities. Recently, decreases in levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c) have been reported in COVID-19 patients (8, 50), indicating a potential pathophysiologic interaction between lipid metabolism and vasculopathy in disease progression. In this review, we will briefly discuss clinical characteristics, particularly dyslipidemia in COVID 19 and provide insights into the speculative underlying mechanisms.

SARS-COV-2 AND CLINICAL FEATURES OF COVID-19

Similar to the SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV-2), SARS-CoV-2 is a positive-sense single-stranded RNA virus and is the newest and seventh known coronavirus that is capable of infecting human beings. SARS-CoV-2 is the causative pathogen for COVID-19 (1). The RNA genome of SARS-CoV-2 has 29,891 nucleotides (GenBank, MN908947), sharing 79% sequence identity with SARS-CoV and 50% with Middle East respiratory syndrome-
related coronavirus (MERS-CoV) (7a, 28). The phylogeny of this coronavirus shows that it is most close to the bat coronavirus (BatCoV) RaTG13, with 96.3% sequence identity (55). The SARS-CoV-2 is considered to be zoonotic (13, 18). However, the intermediate host(s) are yet to be determined. The SARS-COV2 Spike (S) protein, comprised of subunits S1 and S2, is thought to mediate the virus entering host cells via surface angiotensin converting enzyme 2 (ACE2) (28, 47). Host protease transmembrane serine protease 2 (TMPRSS2) promotes SARS-CoV-2 entry of target cells. ACE2 and TMPRSS2 have been found to coexpress in lung type II pneumocytes, ileal absorptive enterocytes, and nasal goblet secretory cells (56), which are thought to be host determinants for viral infection in the initial stage.

COVID-19 patients can be asymptomatic or symptomatic. The incubation period from exposure to onset of symptoms is ~5.1 days. Majority (97.5%) of patients develop symptoms within 11.5 days after infection (23). Pathologically, SARS-CoV-2 can cause damage to almost every vital organ in the body, including the lungs, heart, liver, kidney, eyes, blood vessels, intestines, and brain, with devastating consequences. The virus enters the nose and throat, multiplies within cells and marches down into the lungs, leading to pneumonia. Damage to the lungs can be long term for some recovered patients; this has been observed in surviving SARS patients (53). In serious cases, SARS-CoV-2 injures many other organs and results in deep and systemic damages. Mortality rate of COVID-19 varies in different geographic locations and patient populations, ~13.6% in Italy, and 5.7% in the United States. The time from the onset of symptoms to death ranges from 6 to 41 days (39, 48).

**METABOLIC-ASSOCIATED COMORBIDITIES AND DYSLIPIDEMIA IN COVID-19**

Patients with metabolic-associated preconditions are susceptible to the SARS-CoV-2 attack. A meta-analysis included six studies with 1,527 patients with COVID-19 in China revealed that the proportions of hypertension, cardiovascular/cerebrovascular disorders, and diabetes mellitus were 17.1%, 16.4%, and 9.7%, respectively (24). Wei et al. (49) showed that the main comorbidities in patients in Wuhan were hypertension (32%), diabetes mellitus (12%), and cardiovascular disorders (8%). Although the proportions of these comorbidities in patients in Europe and the United States have been found much higher. In 5,700 patients hospitalized with COVID-19 in New York City, the major comorbidities for patients with COVID-19 are hypertension (56.6%), obesity (41.7%), diabetes mellitus (33.8%), and coronary heart diseases (11.1%) (34). A study including 388 patients in Italy reported the comorbidities are hypertension (47.2%), diabetes mellitus (22.7%), and coronary heart diseases (13.9%) (27), suggesting that metabolic and vascular disorders could have contributive roles in the rapid progression and poor prognosis of affected patients (31). As the studies only analyze the hospitalized patients, the comorbid conditions of asymptomatic and mildly symptomatic patients are unknown, so the overall prevalence of comorbidities in COVID-19 has been not fully established.

More importantly, patients with these preconditions are likely to experience more pronounced symptoms. Guan et al. (15) included 1,099 patients with COVID-19 reported that, compared with severe and nonsevere groups, the proportions of hypertension were 23.7% versus 13.4%, diabetes mellitus 16.2% versus 5.7%, and cardiovascular/cerebrovascular disorders 8.1% versus 1.8%. Another study reported that in 54 nonsurviving patients out of a cohort of 191 patients, the ratios of hypertension, cardiovascular/cerebrovascular disease, and diabetes mellitus were 48%, 24%, and 31%, respectively, much higher than survivors in the same cohort (54). Notably, the overall fatality of patients with no comorbidities is ~0.9%; but the mortality rates for patients with comorbidities are much higher: 10.5% for those with cardiovascular disorders, 7.3% for diabetes, 6% for hypertension (7b), which may be a result of the hyperinflammatory response in a combination with pre-existing endothelial dysfunctions. Patients showed elevations of a series of cancer biomarkers, reflecting acute and diffuse injuries in lungs and probably other tissues as well (49).

One pathogenic cofactor associated with hypertension, obesity, diabetes, and cardiovascular disorders is hypercholesterolemia. The reports about dyslipidemia in patients with SARS are few. One report showed a lower level of TC in patients with SARS compared with healthy subjects (41). Another study reported aberrant lipid metabolism in recovered SARS patients 12 yr after infection (52). These studies suggest that dyslipidemia can occur in patients with coronavirus-related diseases, but the topic has not generated much attention among physicians and researchers. We recently reported dyslipidemia in patients with COVID-19 and demonstrated that the degree of decreased LDL-c was associated with severity and mortality of the disease (8, 50). In a small cohort of 21 patients, lipid profiles were checked before viral infections and during the course of their illness. The levels of LDL-c, TC, and high-density lipoprotein cholesterol (HDL-c) in patients decreased when they were hospitalized and remained low during the treatment. The LDL-c and TC levels recovered to baseline in discharged patients but in those that did not survive, levels decreased continuously (8). In another study of a large cohort of patients (n = 597), lipid data at the time of admission were extracted from the charts of patients with mild, severe, and critical symptoms. LDL-c and TC levels were decreased in patients with COVID-19 compared with the levels from healthy subjects and the degree of reduction correlated with the progression of symptoms (50). HDL-c only decreased in critically ill patients when compared mild and severe cases (50). Thus, LDL-c seems a major player accounting for the dyslipidemia in COVID-19. It was less likely that dyslipidemia in patients with COVID-19 was a side effect caused by interventions, because the patients 1) had decreased LDL-c levels before interventions, 2) received varieties of medications during the disease progression, and 3) had their levels of LDL-c recovered under the same remedies when their symptoms were mitigated (8). Furthermore, a recent proteomic and metabolomic study from the sera of patients with COVID-19 showed a massive suppression of metabolism, including dysregulated levels of multiple apolipoproteins (Apo) such as Apo A1, Apo A2, Apo H, Apo L1, Apo D, and Apo M (14).

Decreased LDL-c, HDL-c, and TC have been reported in many chronic diseases or terminal illness, such as lung cancers (44). Chronic inflammation caused by viral infections may result in dyslipidemia in patients as well. For example, patients infected with human immunodeficiency virus (HIV) show a decrease in HDL-c and increase in LDL-c levels (3, 35); low
levels of LDL-c and HDL-c were shown in patients with chronic hepatitis B infection in the cirrhosis phase (5). In a meta-analysis of nine studies including 1,953 patients, Lima et al. (26) found serum TC and LDL-c levels decreased in patients infected with dengue virus. Moreover, in a 15-yr follow-up multi-ethnic cohort of more than 120,000 adults, Iribarren et al. (20) reported TC was inversely and strongly correlated (or associated) with infections requiring in-hospital treatment or being acquired in the hospital, with the exception of respiratory illness and HIV. Taken together, these reports suggest that chronic inflammation may be involved in the pathological metabolic processing of lipids and ultimately result in the observed dyslipidemia in such patients.

Dyslipidemia in COVID-19 is considered to result from complicated biological and pathological processes triggered by SARS-CoV-2 (Fig. 1). As an acute infectious and inflammatory disease, COVID-19 presents several pathological characteristics that could account for dyslipidemia. Damage of liver function caused by SARS-CoV-2 infection could interfere with LDL uptake and reduce LDL biosynthesis; however, serum liver function tests, including alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP), usually show a moderate increase in less than 50% of patients (8, 49, 50). While this suggests a generally minor effect on patients’ liver function, the levels of these enzymes may not accurately reflect the liver’s ability in regard to LDL synthesis and uptake. Sterol regulatory-element binding proteins (SREBPs) are master transcriptional factors that regulate the expression of a wide range of enzymes required for lipid synthesis. Intracellular lipid homeostasis is regulated by many endoplasmic reticulum (ER) membrane integral sensors such as SREBP cleavage-activating protein (SCAP), squalene monoxygenase (SM), and nuclear factor erythroid 2 related factor-1 (Nrf1), etc. (6, 37, 45). Upon cholesterol deprivation, SCAP will bind to SREBPs in ER, escort them to the Golgi, and facilitate proteolysis of SREBPs, thus resulting in release of SREBP transcription factor domains and entry of nucleus to promote cholesterol synthesis and uptake (45). It is reasonable to speculate that the cholesterol synthesis and uptake pathways have been altered in patients with COVID-19, since recent emerging evidence has shown that SARS-CoV-2 infection can suppress the levels of many proteins related to cholesterol metabolism (4, 14). A thorough investigation will be required in the future to dissect the potential mechanism regarding whether and how SARS-CoV-2 modulates the expressions of these cholesterol sensing proteins in host cells. Second, SARS-CoV-2-induced hyperinflammation in hosts alters lipid metabolism. Inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, have been shown to modify lipid composition, function, and transportation in patients with HIV (9). The COVID-19-associated cytokine storm is thought to be a causative factor leading to fatality in patients with COVID-19. IL-6 was increased in 96% of all patients in our studies (8, 49), suggesting that cytokines may contributes to the abnormality of LDL in our patients. Third, increased vascular permeability caused SARS-CoV-2 infection may lead to a leakage of LDL into alveolar spaces to form exudate, a substance containing high levels of proteins and cholesterol (16, 25). Exudates have been found in lung autopsies from patients with SARS, in cynomolgus macaques infected with SARS-CoV (19, 22, 32), as well as COVID-19 lung pathology (43). Fourth, free radicals signaling, which is generally elevated in host cells with a viral infection (8), accelerates the degradation of lipids in COVID-19. Furthermore, cholesterol provides a platform facilitating the interaction of SARS S protein with ACE2 for entry of targeted cells (12). Adipose/fat tissue may serve as a reservoir for SARS-CoV-2 in patients (36). Finally, a recent study showed that proteins related to cholesterol metabolism decrease in SARS-CoV-2-infected human colon epithelial carcinoma cells, including Apo E, Apo B, LDL receptor related

Fig. 1. Hypothetical interactions among severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), low-density lipoprotein cholesterol (LDL-c), and inflammatory cytokines in patients with coronavirus disease (COVID-19). Outline showing the proposed pathological processes of dissemination of SARS-CoV-2 and the entangled roles of LDL-c and hyperinflammation. Both SARS-CoV-2 and SARS-CoV-2-induced inflammatory cytokines regulate the biosynthesis and metabolism of LDL-c. Simultaneously, adipose tissues can be a potential reservoir for SARS-CoV-2. Inflammation-induced reactive oxygen species (ROS) signaling can facilitate the degradation of LDL-c. The increased vascular permeability by hyperinflammation can promote the LDL-c leakage into alveolar spaces.
protein (LRP), etc. (4). Therefore, SARS-CoV-2 likely imposes a direct impact on lipid metabolism including the endocytosis of LDL-c via LRP. However, whether the level of LDL receptor (LDLR) is altered in patients or not remains unknown, which will need further investigations.

**DYSLIPIDEMIA AND COAGULOPATHY IN COVID-19**

Patients with COVID-19 have shown elevated coagulative and cardiac biomarkers such as D-dimer, fibrinogen, high-sensitivity troponin I, and creatinine kinase–myocardial band (10, 40). Emerging evidence has shown that venous and arterial coagulopathies have been reported with an incidence rate ranging from 8 to 15% in numerous studies, even in an early stage of the disease (17, 21, 27). Thrombotic events can occur in deep veins as well as in lungs, heart and brain, causing pulmonary embolisms, stroke and myocardial infarction (45). The majority of patients with COVID-19 who did not survive had some evidence of coagulopathy (42). All data demonstrate that coagulation activation and endothelial dysfunction are prominent and independent factors underlying the COVID-19 severity and fatality in patients (17), which should be given urgent attention.

A high level of LDL-c is considered a risk factor associated with microvascular dysfunctions in hypertension, diabetes, and cardiovascular disorders (7); such comorbidities exist in more than half of hospitalized patients with COVID-19 in Europe and the United States (27). It is reasonable to postulate that LDL-c contributes to vasculopathy in patients with COVID-19. Endothelial cell (EC) injuries triggering thrombotic events may result either directly from viral infection or indirectly from an effect on ECs lining atherosclerotic areas. For the first scenario, SARS-CoV-2-induced acute endothelial injury could be a factor. Cholesterol has been reported to be necessary for SARS virus replication in early stage in host cells (29). Therefore, it is possible that cholesterol participates in the replication of SARS-CoV-2 in host cells, including ECs. The high virulence of SARS-CoV-2 to the infected ECs could cause acute and local blood vessel injuries, thus triggering coagulopathies as significant clinical sequelae. For the second scenario, accumulation of LDL in the subendothelium, where oxidative modifications on LDL occur, becomes an early step in atherogenesis (30, 51). Vulnerable plaques with enrichment of inflammatory cells and lipids will release highly thrombogenic contents and trigger an atherothrombotic occlusion upon being ruptured (11, 38). One speculation is that the ECs within atherosclerotic plaques are more vulnerable to an attack from SARS-CoV-2 or inflammatory storms, causing a rupture of plaques, and a high risk of developing coagulopathy in patients with cardiovascular associated preconditions.

Remedies for active management of LDL-c levels such as statins may be beneficial to those patients with COVID-19 who have preconditions of hypertension, obesity, diabetes, and cardiovascular disorders. Hyperlipidemia is a significant contributor to endothelial dysfunction leading to atherosclerosis. Lowering LDL-c levels will reduce the degree of vasculopathy and thus protect the endothelial integrity from SARS-CoV-2 attack. Furthermore, it will be reasonable to postulate that SARS-CoV-2 can utilize cholesterol for multiplication, a mechanism that SARS-CoV has shown in the host cells (29).

Therefore, decreases in cholesterol may be helpful to mitigate SARS-CoV-2 replications and viral load in patients.

Collectively, dyslipidemia in COVID-19 may be a result of complex metabolic and pathophysiological processes. Given the dysregulated levels of LDL-c, malfunctioning ECs, thrombotic event, and the high incidence of metabolic-associated preconditions in patients with COVID-19, the contributive roles of LDL-c should not be underestimated. Future studies should investigate the correlation between high plasma LDL-c levels and the incidence of development of severe symptoms and the mechanisms by which LDL-c can facilitate and accelerate vasculopathy synergistic with SARS-CoV-2.

**GRANTS**

Funding this work was supported by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (Grant AR073172 to W.T.).

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

X.C. and R.Y. prepared figures; X.C. and W.T. drafted manuscript; X.C., R.Y., H.A., D.F., and W.T. edited and revised manuscript; X.C., R.Y., H.A., D.F., and W.T. approved final version of manuscript.

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