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Review

Relationship between COVID-19 and HDL dysfunction

Esin Eren[1, 2], Esra Akıdan[1], Mehmet Tugrul[1], Necat Yilmaz[1]
[1]Department of Clinical Biochemistry and LC/MS-MS Laboratory, Antalya Training and Research Hospital
[2]Department of Clinical Biochemistry, Bilim University Health Science, Antalya, Turkey

Abstract

Recent data show that no age group is excluded from the possibility of SARS-CoV-2 infection. However, it is more likely to affect the elderly with comorbidities such as cardiovascular and pulmonary diseases, diabetes, and hypertension that can lead to the progression of COVID-19. Dyslipidemia is often found with these comorbid diseases. According to recent findings, lipoproteins, and particularly high- density lipoprotein cholesterol (HDL-C), may play a role in regulating the entry of the SARS-CoV-2 virus into the host cell.

In fact, HDL-C has many beneficial properties, including anti-inflammatory, anti-oxidative, anti-thrombotic, anti-infectious, anti-apoptotic, intercellular communication, and pro-vasodilator capacities. HDL-C has an affinity for binding and neutralization of the pathogen. The link between COVID-19 and lipid-dependent pathologies has not yet been fully understood. We draw attention to the molecules and functions involved in HDL-C. Because many therapeutic compounds that regulate HDL-C functions and metabolism can be used in the treatment of COVID-19 recently.

Keywords

SARS-CoV-2; COVID-19; HDL; Dsylipidemia; Pneumonia

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Corresponding Author: Necat Yilmaz, SBU-AEAH–LC-MS/MS Toxicology Laboratory, Kazim Karabekir street, Muratpasa, Antalya, Turkey.
E-mail: necatyilmaz@hotmail.com P: +90 5053578305
Corresponding Author ORCID ID: https://orcid.org/0000-0002-3865-9156

SARS-CoV-2

It belongs to the beta genus of the coronavirus family, which causes COVID-19 and is called severe acute respiratory syndrome (SARS) coronavirus-2 (SARS-CoV-2). In fact, the SARS-CoV-2 virus is the 7th known member of the coronavirus family that infects humans [1]. SARS-CoV-2 initially enters the epithelial cells of the upper respiratory tract and reproduces, on the contrary, this phenomenon is not significantly observed in SARS-CoV [1,2]. This diverse process likely explains the relatively high viral load in the upper respiratory tract, the increased levels of viral transmission, and the significantly higher contagiousness. The SARS-CoV-2 virus and its homologue, SARS-CoV, penetrate human cells through the binding of viral spike protein and human angiotensin converting enzyme II (ACE2). High fever, which is one of the symptoms of the disease, is one of the measures to reduce the ACE2 receptor binding rate due to increased body temperature [2].

Current evidence indicates that systemic microvascular damage and immune thrombosis play a key role in the pathogenesis of COVID-19 [3]. Similarly, circulating megakaryocytes and microthrombi are prominent due to increased micro-thromboembolism in many organs. Of course, the ACE2 receptor is widely expressed in all vascular endothelial cells, thus providing a potential explanation for the finding that COVID-19 is associated with hypercoagulation [3].

HDL-C Functions

In addition to the many functions of HD-C, its main task is to promote reverse cholesterol transport (RCT) from the environment to the liver. In addition to this anti-atherosclerotic RCT function of HDL-C, functions of HDL-C include modulation of the immune system and control of infectious diseases. Thus, HDL-C functions also consist of immune-modulating, anti-infectious, anti-thrombotic, anti-apoptotic and antioxidant functions [4]. Pneumonia in general is an important public health problem worldwide with its high incidence and one of the most common infections leading to hospitalization [5]. Dyslipidemia, which is increasing in societies today, has been defined as a marker of severe pneumonia for a long time. As a result, decreased HDL-C levels have been reported with increasing infections in clinics and especially in intensive care patients [5,7]. In fact, HDL-C particles have a great affinity for binding and neutralization of pathogen-associated lipids (e g, lipopolysaccharide, lipoteichoic acid) that mediate excessive immune activation in sepsis [8].

The clearance of the SARS-CoV-2 in the human body is one of the important indicators for the recovery of COVID-19 patients. A study conducted during the COVID-19 pandemic to clear this virus showed that HDL-C may be associated with disease severity and mortality [9,10]. What is well known for now is that low HDL-C and total cholesterol (TC) concentrations show an association between COVID-19 infections in patients. In contrast, an increase in triglycerides (TGs) may be seen in patients infected with SARS-CoV-2 [11]. In conclusion, dyslipidemia, low HDL-C, and high TGs can be considered associated with the risk of developing pneumonia in the future [9, 12].

Indeed, the positive role of HDL-C in the innate immune response is now well known. Since immune modulatory molecules in the structure of HDL-C play a role in complement activation and acute inflammatory response, a relationship between pneumonia and dyslipidemia should be expected in severe form of COVID-19 [13]. For example, there is promising literature on whether HDL-C affects virus clearance in the human body, as discussed above. This recent study found that the replication cycle time of the SARS-CoV-2 viral nucleic acid was shorter in the low HDL-C group compared to the normal group [9].

Undoubtedly, liver cells can be damaged during COVID-19, such that HDL-C is synthesized the liver in large quantities. We cannot rule out that HDL-C may decrease quantitatively and qualitatively, often due to impaired liver function in COVID-19 disease [4, 13, 14].

(S) Protein

Clinical data obtained from COVID-19 point to the presence of serious cardiovascular complications in addition to severe pneumonia [15, 16], because the excessive inflammatory response (cytokine storm) in COVID-19 is thought to be the primary cause of treatment failure. Whereas, although the inflammatory response represents a host defense against pathogens, this process is beneficial as long as it is limited to local infection control [17]. When the inflammatory response in COVID-19 is excessively disproportionate, systemic inflammation may lead to diffuse intravascular coagulation, respiratory distress or septic shock, and increased morbidity mortality in COVID-19 patients (Yilmaz N, Eren E. COVID-19 iron ferroptosis parafibrin. Available at: www.researchgate.net/publication/341055648) [16].

As far as is known, the SARS-CoV-2 virus can enter the cell by binding to ACE2 and some other receptors (CD147 etc.) of the pointed glycoprotein (S protein) in host cells [18,19]. In addition to these differences in tropism, the 10–20-fold higher affinity compared to SARS-CoV makes ACE-2 receptors targets for SARS-CoV-2 [18]. Since cellular polyproteinconvertases such as (S) protein's, furin and capesin not found in SARS-CoV could potentially increase the uptake of SARS-CoV-2 via ACE2 receptor via endocytosis [19,20]. Published data indicate that the protein of the SARS-CoV-2 virus (S) alone can damage the endothelium through increased glycolysis with impaired mitochondrial function and eNOS activity. This is due to the fact that SARS-CoV-2 virus infection triggers mitochondrial ROS production in the vascular endothelial tissue and can induce glycolysis [21-23]. However, functional HDL-C tries to protect the ACE2 receptor system in vascular tissue. But the vascular endothelial system becomes infected with SARS-CoV-2. As a result, all organs especially endothelial cells can be damaged by the qualitative and quantitative reduction of HDL-C [4, 13, 16, 17].

HDL-C has not only quantitative but qualitative laboratory measurements. Indeed, HDL-C in endothelium contributes significantly to vascular tone. Also, HDL-C contributes to the production of nitric oxides (NOs). HDL-C also has NOs independent properties on endothelial cells; these are induced proliferation, increased barrier function, suppressed inflammation and decreased apoptosis [4, 16].

But, the anti-inflammatory and antioxidant properties of HDL-C are significantly reduced during viral infections such as influenza and HIV infection. Unfortunately, after the acute onset

of COVID-19, low TC levels accompanied by low HDL-C have been reported [14].

Also, HDL-C may mediate anti-viral effects through interaction with the scavenger receptor SR-BI, which causes a decrease in inflammatory protein production and an increase in pro-angiogenic growth factors by activating the PI3K / Akt pathway. However, the decreased ACE2 receptor functionality over time in severe COVID-19 may cause it to lose its unique protective effect on the vascular endothelial system [24,25].

Whereas HDL-C that can pass into the vascular sub-endothelial space in healthy people can preserve its endothelial structure, but unfortunately, as a result of the increased cytokine storm in COVID-19, and especially pro-inflammatory cytokines such as IL-6 may prevent the transition of HDL-C to the endothelium [26-28].

Numerous in vitro and in vivo studies have now demonstrated the anti-inflammatory and pro-angiogenic effects of HDL-C on endothelial cells [29]. HDL-C functions may be important not only for endothelial cells, but also in the regulation of macrophage activity. In COVID-19, macrophages may show mitochondrial insufficiency as a result of increased metabolic needs after infection, and thrombotic complications may occur as a result of vascular dysfunction. In addition, macrophages can be loaded with excess free iron in the environment.

HDL-C may contribute to the reduction of mortality and morbidity in COVID-19 by reducing the inflammatory response caused by over activation of pathways in the immune system [29]. COVID-19 can transform HDL-C into a dysfunctional, pro-inflammatory particle as a result of "cytokine storm" and severe inflammation in COVID-19 [4]. Thus HDL-C can be damaged qualitatively and quantitatively in COVID-19 [16, 30].

HDL-SR-B1 Receptors

In the literature, a study supports the main idea of this article because the study showed that SR-B1, the major receptor of HDL-C, facilitates entry of the SARS-CoV-2 virus binding to ACE2 [31]. Thus the activity of the (S) protein to the ACE2 receptor may be associated with the cellular uptake of HDL-C. However, as is known to date, SR-B1 is not only the HDL-C's receptor, but also mediates the selective uptake of cholesteryl-esters and is its receptor at other lipid components [31]. According to these findings, the presence of ACE2 and SR-B1 expression on the surface of many tissues and cells affected by COVID-19 may increase the effect of the virus. Especially, the SR-B1 receptor system in the lungs may play a role in pulmonary inflammation [31]. It is noteworthy that SR-B1 could be a potential therapeutic target that could interfere with SARS-CoV-2 infection [11]. In addition, according to the data obtained, cholesterol abundance in the host cell plays an important role in viral entry and fusion. Perhaps many drugs that have been used for many years to combat atherosclerosis may be effective in the treatment of COVID-19 [32]. As is known, obesity, atherosclerotic diseases and diabetes in which the SR-B1 receptor is active are comorbid conditions that increase the risk of developing COVID-19 disease. Researchers have been increasingly successful in uncovering the possible link between the severe inflammatory response seen in COVID-19 and HDL-C dysfunction seen in COVID-19 comorbid diseases [33-35].

HDL-Apo-A1

Lipoprotein Apo-A1 undoubtedly constitutes the largest amount of more than 200 proteins in the HDL-C structure [36]. Apo-M, which is found in HDL-C structure like Apo-A1 but plays a very small role in HDL-C function, is associated with the Toll-like receptor and T cell receptor in macrophages [34,38].

Also, lipoproteins in the structure of HDL-C play a very important role in protecting the endothelium against infection [36, 37]. In a published study, they showed in the general population that Apo-A-1, which constitutes 70% of the HDL-C structure, decreased with the SARS-CoV-2 outbreak [38]. This is a very important finding that COVID-19 can affect the proteins involved in HDL-C structure.

Statistically, the area Under the Characteristic Curve (diagnostic value; AUC: 0.98) of Apo-A1 was also found to be very high in the COVID-19 epidemic. In addition, intensive care attendance and survival rates were found to be associated with Apo-A1 values [38].

Decreased Apo-lipoprotein expression may underlie the relationship between COVID-19 and Apo-A1, because hepatic Apo-lipoprotein gene expression may be suppressed in the COVID-19 disease [36,39]. Restoration of lipoprotein function with ApoA-I enhancing agents can thus be valuable in the treatment of COVID-19 [31, 36, 38].

Recently, it has been reported that Apo-E, another lipoprotein in the HDL-C structure, and the increase in phospholipid transfer protein (PLTP) activity in the HDL structure accelerate recovery in intensive care patients [39-48].

Various findings suggest that deficiencies in Apo-E function may be important in the association of SARS - CoV - 2 with dyslipidemia and may avoid complications because Apo-E is expressed in alveolar epithelial cells as well as lung macrophages [42-44].

Supporting this knowledge, it has been reported that the Apo-E4 variant predicts the severity of COVID-19 [44,45]. Most of the Apo-E in the blood is produced by the liver, but macrophages are responsible for producing 5-10% of Apo-E in plasma [45.46].

Both the liver and macrophages are affected in COVID-19 disease, so changes in the Apo-E level in the HDL-C structure can naturally be expected. This information becomes even more important when considering COVID-19 bio-pathology [46]. Low ApoA-I and Apo-E levels in COVID-19 patients may be partially responsible for lung inflammation [45, 46].

HDL-miRNAs

In addition, HDL-C prevents the oxidation of LDL-C, therefore sufficiency of Apo-AI, the activity of LCAT, lipoprotein-related phospholipase A2 (Lp-PLA2) and paraoxonase 1 (PON1) are required [4,16,36]. The HDL-C ability to prevent oxidant damage through protein and enzymes in its structure is also supported by the selective removal of lipid hydroperoxides and hydroxides by hepatocyte SR-BI [4,36]. HDL-C also participates in intercellular nucleic acids communication through transfer between tissues [47]. Recently, HDL has been reported to carry miRNA, small non-coding RNAs that bind to complementary target regions in the 3 'untranslated region of mRNAs, suppressing gene expression, thereby inhibiting translation and inducing mRNA degradation. and to endothelial cells [47,48]. However, research is needed to

determine the effect of HDL-C linked miRNAs in humans and animal models in the context of severe inflammatory diseases such as COVID-19.

HDL-Innate immunity

HDL-C also contributes to innate immunity by modulating immune cell function. However, this hypothesis has not been extensively studied in the context of COVID-19 because HDL-C is also anti-infectious, anti-parasitic, and anti-viral.

Indeed, HDL-C has the unique capacity to prevent endotoxic shock, readily binds to lipopolysaccharides (LPS), and contributes to removing LPS through biliary excretion, thus aiding innate immunity [48,49].

HDL-C Anti-thrombotic activity

In addition to respiratory symptoms, abnormal coagulation with thromboembolic disease is thought to be an important factor in COVID-19 worsening and clinical outcomes. In this regard, the formation of parafibrin due to the impairment of iron metabolism may play an important role (available at: www.researchgate.net/publication/341055648). High ferritin levels seen in COVID-19 may lead to dyslipidemia [16, 50, 51]. As expected, HDL-C has anti-thrombotic activity, suppressing the coagulation cascade and inhibiting platelet activation, but also has the function of reducing platelet hyper-reactivity by limiting intra-platelet levels of cholesterol overload. Thus, HDL-C may have a limiting effect on micro-thrombi that can be seen in the pathogenesis of COVID-19 [16,52].

HDL-LCAT

Lecithin cholesterol-acyl-transferase (LCAT), which is in the structure of HDL-C, is another important anti-infectious molecule. In fact, LCAT plays an important role in cholesterol metabolism as it is the only extracellular enzyme that can esterify cholesterol. LCAT activity ensures the maturation of HDL-C's by esterifying their cholesterol. At the same time, LCAT is the strongest activator of Apo-AI, the main protein component of HDL-C. Activity of LCAT in viral infections can prevent the development of hypertriglyceridemia [53].

Although LCAT activity has not yet been measured in COVID-19, in many viral infections, LCAT activity has been reported to decrease significantly, and thus Apo-AI levels have decreased compared to healthy controls [54]. Perhaps decreased levels of Apo-A1 in COVID-19 patients are associated with reduced LCAT activity. Additionally, viral infections that affect LCAT enzyme functionality can result in a serious decrease in plasma HDL-C levels and significant clinical consequences. It is thought that the LCAT enzyme can stimulate the Apo-AI strands during maturation by binding and therefore affects HDL-C function [54,55]. In addition, similar to COVID-19 disease, there may be a relationship between LCAT and HDL-C functions with blood groups [56]. This situation is similar to COVID-19 disease because studies show that individuals with non-O blood groups, which can impair HDL-C function, are at greater risk of COVID-19 [57].

HDL-SAA

Inflammatory factors such as SAA in the HDL-C structure may, unfortunately, increase with COVID-19 disease. In this case, HDL-C structural character may change and transform into a pro-inflammatory dysfunctional HDL-C form [16]. Since SAA is a non-specific acute phase protein, its synthesis can be stimulated by many cytokines (IL-1β, IL-6 and TNF-α), which may increase in COVID-19 disease [58]. In some recent studies, the SAA molecule has been shown as a biomarker for assessing the severity and prognosis of the disease in COVID-19 patients. The increase in SAA in COVID-19 is undesired because SAA can further increase the inflammatory response by activating chemokine and inducing chemotaxis even at a very low concentration [58, 59]. Studies show that patients infected with COVID-19 have large amounts of IL-1β, IFN-γ, IP-10, MCP-1, which in turn, stimulate liver cells to produce SAA [60]. In addition, SAA can increase neutrophils survival and subsequently increase the inflammatory response through the P2X7 receptor, an ion channel of neutrophils. In addition, aging, which is an important risk factor in COVID-19, generally causes an increase in SAA levels, on the contrary, HDL-C levels and functions may decrease in elderly people [58, 62].

HDL-PON1

The PON1 enzyme, which is in the structure of HDL-C, is associated with the antioxidant function of HDL-C. In COVID-19 disease, due to higher inflammation and oxidative stress, there may be PON1 consumption in the structure of HDL-C. For example, it has been reported that HDL-C loses its anti-oxidant properties during infection with influenza A [63, 64]. In future clinical trials, the possible role of the PON1 enzyme in COVID-19 will be better understood. Thus, supportive applications that can increase PON1 enzyme activity in COVID-19 can be included in the treatment [4, 16, 63, 64].

HDL-Ferritin

Hyperferritinemia is one of the cardinal laboratory findings of COVID-19 disease. Hyperferritinemia may negatively affect HDL-C functions in COVID-19 disease [65,67]. The cellular function of ferritin is to store iron in a non-toxic and bioavailable form [65]. Thus, at the same time, ferritin, the cellular storehouse of iron, is a key molecule in the immune system that regulates cellular defense against inflammation [65,66]. Ferritin consists of two different subunits named according to their molecular weight: H "heavy" and L "light". The ratio of H and L subunits is tissue dependent. In particular, the ferritin H subunit participates in the catalytic oxidation of FeII to FeIII (ferroxidase), while the L-subunit provides the nucleation sites for bioavailable storage of the FeIII product [65,66]. In addition, hyperferritinemia is an important mediator of immune dysregulation [65,67].

Generally, ferritin may be higher in elderly and male patients. In addition, decreased HDL-C function is a common finding in elderly and male patients [68-72].

Possibly in COVID-19, excess iron retention in macrophages may be increased through transferrin receptors or HDL-C related SR-B1-mediated by erythro-phagocytosis.

Thus, pathway may lead to a significant increase in both mRNA and protein levels in ferritin synthesis [16, 73].

While iron-loaded macrophages can release both iron and ferritin through exocytosis, ferritin excretion from cells can be significantly reduced if there is not enough HDL-C in the environment [73, 74]. Finally, a broad neutralizing antibody response using synthetic ferritin that cheats the SARS-CoV-2 virus had been reported [74] because, according to the findings, iron metabolism parameters deteriorate in patients who receive

outpatient and inpatient treatment in COVID-19 disease. Compared to mildly affected COVID-19 patients remaining at the outpatient level, the inpatient cohort shows a significantly more pronounced irregularity in iron metabolism parameters [75,77]. Moreover, hepcidin may increase in COVID-19 patients due to IL-6 stimulation, and elevated hepcidin levels may have adverse effects on HDL-C functionality [76,79].

According to different experimental septic models, reconstructed rHDL infusions may be a treatment option to reduce inflammation in septic patients. While a similar usage option may apply to Apo-A1 mimetics in sepsis. Nowadays although there are still few articles in the literature, functions of HDL-C can be considered a potential therapeutic target for the SARS-CoV-2 virus [56, 80, 81].

Treatment options

Although it may seem distant to us, studies on the origin of SARS-CoV-2 agree that the virus probably originated from the bat because analysis of mutations at contact sites in the SARS-CoV-2 virus receptor binding site reveals that human sensitivity is more likely to occur in Pangolin [19, 20]. Unfortunately, HDL-C can gain pro-inflammatory properties by losing its useful properties in severe inflammatory diseases. For example, in the case of HDL-C dysfunction, the loss of cholesterol output capacity by RCT from macrophages, in COVID-19 disease may cause an already increased macrophage load, so the activity of macrophages may be reduced. HDL-C functionality and PON1 enzyme activity are required in the face of increased inflammation and high oxidative stress in COVID-19 disease. Moreover, in COVID-19 disease, changes in the content of bioactive lipids or oxidative modifications in lipids and protein load of HDL-C can cause erythrocyte damage. Also, the reduction of erythrocytes that can be seen in COVID-19 disease may occur as a result of the reduced ability of the erythrocyte membranes' to metabolize hydroperoxides.

The "cytokine storm" underlying COVID-19 disease, low HDL-C, high lipoprotein oxidation, and low Apo-E levels can produce immune-mediated inflammatory dyslipoproteinemia. With clinical and laboratory studies to be carried out in the upcoming period, the origin and pathophysiology of SARS-CoV-2 will be better understood and appropriate treatment strategies for COVID-19 disease will be developed. For example, futuristic use may apply to Apo-A1 mimetics in COVID-19 disease. HDL-mimetic agents could enhance the normal reverse lipid transport system (RCT). Also, ApoA-I mimetic peptides might improve endothelial cell functions [80, 81]. Finding that hepcidin is up-regulated by the inflammatory cytokine IL-6 in COVID-19 may be one of the treatment options. However, clinically used drugs that can block this relationship (Siltuximab, Tocilizumab) [77,78,81] are valuable. In addition, using drugs to down-regulate hepcidin using RNA antibodies that block ferroportin has been described [81].

Conclusion

In addition, endothelial tissue, which can be disrupted by SARS-CoV-2 viral invasion in COVID-19, can reduce vasodilation by reducing NO production. HDL-C may be required to maintain NO production in the vascular endothelial cells. In addition, pro-inflammatory HDL-C may, unfortunately, increase the greatly enhanced monocyte chemotactic activity in COVID-19 disease. In HDL-C dysfunction, its capacity to block NADPH oxidase activity and superoxide production may decrease. In general, higher membrane cholesterol may facilitate cellular entry of the SARS-CoV-2 virus. The modulated efficiency of viral entry can be explained by the presence of the SR-B1 receptor [80,81]. HDL-C itself appears to have a variety of roles from being a

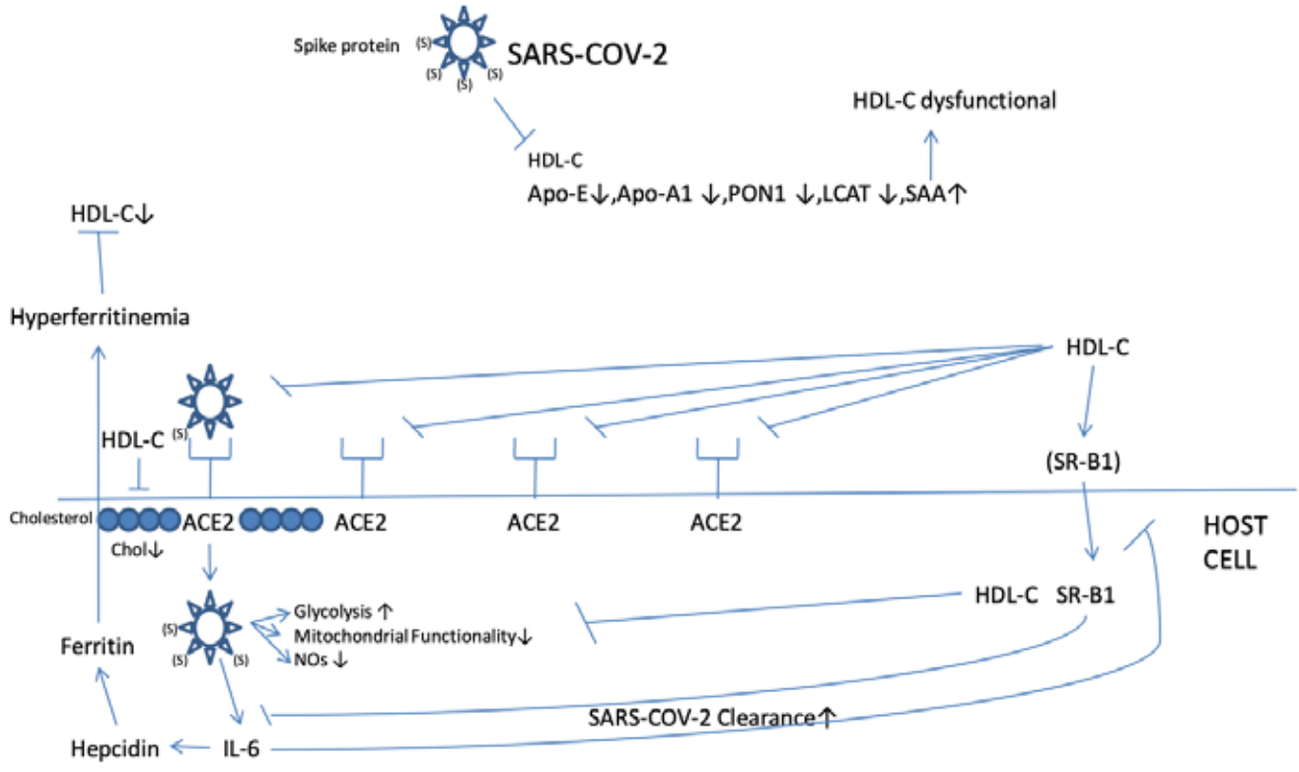

Figure 1. Possible pathways of the SARS-CoV-2 virus on HDL-C functions

scavenger, an immune modulator, and a viral entry vehicle for viruses. It should also be kept in mind that HDL-C suppresses cytokine inhibition in inflammatory cells. As a result, HDL-C functions and composition can be targeted to selectively inhibit the life cycle of the virus as the basis of antiviral therapy. At the same time, HDL-C can be a potential biomarker for monitoring SARS-CoV-2 viral infection status [81].

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

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All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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