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Original Research Article

LDL in COVID-19 - Un Update

Athina Myrou[1*], Theodoros Aslanidis[2], Vasileios Kachtsidis[1], Christina Kiouli[1], Christos Savopoulos[1]

[1]First Propaedeutic Department of Internal Medicine, AHEPA University Hospital, Thessaloniki, Greece
[2]Intensive Care Unit/Anesthesiology Department, "Agios Pavlos" General Hospital, Thessaloniki, Greece

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***Corresponding Author:** Athina Myrou
First Propaedeutic Department of Internal Medicine, AHEPA University Hospital, Thessaloniki, Greece

Abstract

Lipids are indispensable in the SARS-CoV-2 infection process and studies have focused on investigating the clinical significance of plasma lipid profile on COVID-19 patients. There are studies in patients with COVID-19 that document that blood lipid levels change in individuals who have been infected by SARS-CoV-2 and that their increase is consistent with the degree of morbidity and mortality. At the same time, it has been measured that during the complete recovery of the patients there is also a complete normalization of the lipid profiles. Furthermore, it has been reported that a large proportion of COVID-19 patients continue to receive lipid-lowering therapy after recovery. Lipid-lowering medication is generally continued throughout the period of active infection and beyond. The present review focuses on investigating the relationship between low-density lipoproteins (LDL) and SARS-CoV-2 infection and how lipid levels can predict prognosis or mortality in patients with COVID-19.

Keywords: LDL, COVID-19, lipid profile, lipid-lowering medication, biomarker, mortality.

INTRODUCTION

In the process of infection, lipids play a critical role as they are important structural components of cellular and subcellular organic membranes. The internalization of the virus requires the attachment of the virus to the host cell membrane and activates an endocytosis mechanism, where this process is influenced by membrane lipid composition (Abu-Farha M *et al*., 2020). Cholesterol is being recognized as a molecule involved in regulating the entry of the SARS-CoV-2 virus into the host cell and generally, higher membrane cholesterol coincides with higher efficiency of COVID-19 entry (Kočar E *et al*., 2021).

There are research data that have revealed a decrease in total cholesterol, LDL-C, HDL-C, and apolipoprotein B and A-I levels in patients with COVID-19 (Fan J *et al*., 2020, Hu X *et al*., 2021, Tanaka S *et al*., 2021, Wang G *et al*., 2020, Wei X *et al*., 2020). In primarily infected patients who visited Wuhan on the outburst of COVID-19 the levels of serum TC, HDL- and LDL-cholesterol were significantly lower, and the level of HDL-cholesterol was more significantly altered (Hu X *et al*., 2020). On another study, patients with COVID-19 showed lowered levels of blood cholesterol, high-density lipoproteins (HDL) and low-density lipoproteins (Kočar E *et al*., 2021). At the same time, the reduction was proportional to the severity of the disease and LDL-C and HDL-C levels were inversely correlated with C-reactive protein (CRP) levels (Feingold KR *et al*., 2022). Important is the fact that it has recorded a complete restoration of serum lipid levels with the patient's recovery.

In the case of patients with COVID-19, lipids, especially LDL-C and HDL-C, play an important role as they continuously interact with the lipid rafts in the host cell membranes and can modify the interaction of virus with host cells and the resultant disease severity. Documented reduction in lipid levels in patients with COVID-19 appears to correlate with disease severity and mortality prognosis. Consequently, the investigation of the role of lipids in the pathogenesis of COVID-19 may contribute as a prognostic factor of the patient's clinical course (Ballout RA *et al*., 2021).

EXPERIMENTAL SECTION/MATERIALS AND METHODS

How Covid-19 infects the cells

Coronaviruses are enveloped viruses with a positive-stranded RNA genome made up of the nucleocapsid (N), membrane (M), envelope (E) and spike (S) proteins, which are structural proteins (Joerg

Glende *et al*., 2008). The first step in infection is the entry of nucleocapsid into the host cell membrane. Protein S (spike protein) plays an important role in the initiation of the infection as the glycoproteins in the virus 'characteristic "crown" of spikes enable its viral entry into human cells via receptor-mediated plasma membrane fusion - subunits S1 for receptor binding and S2 for membrane fusion, as recent studies have shown that spikes require cholesterol to enter cells (Joerg Glende *et al*., 2008). Specifically, SR-B1 can help S1 spike subunit to bind to HDL and promote the entry of SARS-CoV-2. This has been shown by in vitro studies where membrane cholesterol increased the number of viral entry sites on the host cell membrane and the number of angiotensin-converting enzyme 2 (ACE2) receptors in the membrane fusion site (Joerg Glende *et al*., 2008).

Infection and Covid-19 patients

Lipoproteins are the first line of defense against microbes. Most lipoproteins neutralize bacterial membrane Gram-negative and Gram-positive components (Kočar E *et al*., 2021). Additionally, in the form of lipoproteins serves as a carrier of antioxidants, drugs etc. It has been noticed that enriched lipid rafts provide a better environment for viruses to enter the host cell by endocytosis (Kočar E *et al*., 2021). In vitro studies have shown that cholesterol can increase the number of endocytic entry points. However, we know through Imhoff *et al*., that the cholesterol dependence is a property of the S protein and independent of other viral proteins (Yan Tang *et al*., 2021).

Endocytosis is a cellular process which aids in intracellular trafficking and endosomal formation in transportation of molecules for essential signaling within the cell. Liver X receptors (LXR) regulate essential lipid homeostasis by regulating cholesterol, which is essential as cholesterol levels must be balanced otherwise it could be toxic (Mettle Brahma *et al*., 2023).

Cholesterol is an important component of lipid rafts that fills the gap between the associated sphingolipids which makes the lipid raft more resistant to washing. The binding of cholesterol and saturated lipids promotes the formation of lipid rafts, which have a higher affinity for certain proteins and lipids. We know that one of the many cellular processes of cholesterol is regulating the entry of viruses into the host cell. Patients with lipid-associated pathologies have different infections process as well as reaction to the virus (Yan Tang *et al*., 2021).

During the study of Wang *et al*., it was shown that using cholesterol from serum to increase the cholesterol in cell membranes could enhance the ability of the virus to infect and both the number and apparent diameter of GM1, lipid rafts (which is the number of viral entry points of ACE2) on cholesterol- loaded cells increased. It was also shown that cholesterol can simultaneously transport ACE2 to the endocytic entry point effectively utilizing it to enter cells. Meaning that the number of endocytic entry points cholesterol may increase the entry of pseudo-SARS-CoV-2 by increasing the number of endocytic entry points and transporting ACE2 to the endocytic entry point (Yan Tang *et al*., 2021).

It is well recognized that gram positive and gram-negative bacterial infections result in changes in plasma lipid levels. They decrease total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels as well as apolipoprotein A-I, A-II, and B levels. This is done either by elevated triglyceride levels or normal levels that are too normal for the decreased nutritional status that accompanies infections. Cholesterol in macrophages of cardiovascular disease (CVD) patients activates NLRP3 and an inflammatory state that provides involuntary favorable conditions to the infection of SARS-CoV-2, leading to poorer prognosis for such patients, compared to this without CVD. So, increased cholesterol levels are beneficial to the virus 'entry to the cells, but when the organism is infected, it results in lowered levels of lipid levels which were more prominent in severe cases of infection (Kenneth R Feingold *et al*., 2021).

DISCUSSION

Patients with Covid-19 and LDL

In patients with COVID-19, a decrease in HDL particles, particularly low numbers of small HDL particles and a predominance of small LDL particles compared to larger LDL particles, has been identified (Ballout RA *et al*., 2021). The lower the HDL-C and LDL-C levels are, the greater the severity of the COVID-19 infection is (D'Ardes D *et al*., 2021, Sun JT *et al*., 2020) while decreasing LDL-C levels has been associated with severity and mortality (Mahat RK *et al*., 2021).

It is known that in acute infection or severe illnesses lower LDL cholesterol are presented and a tendency for triglycerides to rise and for HDL cholesterol to decrease. LDL cholesterol usually presents complete normalization as the acute illness abates. However, in chronic inflammation the increase in triglyceride and decreased HDL mainly because of inflammatory cytokines (Chidambaram V *et al*., 2022) and is a possibility for patients with COVID-19 even after recovery. Dyslipidemia is also present in cases of patients with COVID-19 as is evident in various injuries of the human system (cardiovascular, immune, and respiratory systems). The development of dyslipidemia is associated with the significant increase in the levels of pro-inflammatory cytokines, which is present in patients with COVID-19 and therefore justifies the impaired lipid regulation (Mohammadshahi J *et al*., 2023). In the study by Stasi *et al*., (Stasi A *et al*., 2021) it was revealed that critically ill patients admitted to the intensive care unit showed features common to sepsis, namely changes in

the lipid profile and exaggerated systemic inflammatory response. The effect of dyslipidemia on renal injury and dysfunction is associated with a high risk of mortality and long-term complications.

Xu, Xie & Al-Aly (Xu E *et al*., 2023) found in their study increased LDL cholesterol, triglycerides, total cholesterol, and decreased HDL cholesterol in patients who survived COVID-19 and compared to individuals who never tested positive for COVID-19. The degree of dyslipidemia was greater in patients where the infection was more severe and required admission to the intensive care unit. Besides the fact of reduced total cholesterol, LDL cholesterol and HDL in patients with COVID-19, an increased risk of dyslipidemia has also reported for the post-acute phase of COVID-19 of up to 6 months. Studies has shown a higher blood cholesterol and LDL concentrations 180 days after patient's first positive PCR test while there is a risk of dyslipidemia at 12 months on survivors. This risk includes elevated total cholesterol, triglycerides, LDL cholesterol (LDL>130 mg/dL) and reduced levels of HDL cholesterol (Xu E *et al*., 2023).

An observational cross-sectional study examined the association of the plasma lipid profile with SARS-CoV-2 infection clinical evolution on 1.411 COVID-19 patients (Masana L *et al*., 2021). The result showed that a severe outcome was associated with lower HDL cholesterol levels and higher triglycerides and as a result the lipid profile should be considered as a sensitive marker of inflammation and should be measured.

Aydin *et al*., (Aydın S *et al*., 2022) have investigated the relationship between lipid levels and mortality in 5274 patients hospitalized for COVID-19 infection. A statistically significant association between LDL-C, HDL-C, and TG levels and the risk of death has been found, while low HDL-C and high TG levels were negatively associated with COVID-19-related mortality. This shows that blood lipid levels can be useful in predicting mortality in patients with COVID-19.

Aparisi's (Aparisi Á *et al*., 2021) retrospective single-center study evaluated the association of lipid markers with 30-days all-cause mortality in 654 COVID-19 patients. Their results have shown that low LDL-c serum levels are independently associated with higher 30-day mortality in COVID-19 patients. Those patients who survived presented complete normalization of their lipid profiles on short-term follow-up and thus hypolipidemia in COVID-19 infection may be secondary to an immune inflammatory response.

COVID-19 patients in Fabre (Fabre B *et al*., 2022) study presented higher glucose, TG, TG/HDL-cholesterol, and RLP-cholesterol levels, but lower total, LDL, HDL and no-HDL-cholesterol levels. Lower levels of all the cholesterol fractions were related with the presence and severity of COVID-19, indicating a lipid metabolic disorder in COVID-19 patients. It has also been reported that patients with COVID-19 present a prevalence of hypercholesterolemia as a comorbid condition (Iqbal Z *et al*., 2020).

The study of Rohani-Rasaf (Rohani-Rasaf M *et al*., 2022) showed in patients with a severe clinical course of the disease and in the deceased patients significantly reduced levels of TC, HDL-C and LDL-C compared to patients with a mild clinical course or in the survivors. At the same time, similar results were revealed by meta-analyses leading to the conclusion that TC/HDL-C and LDL-C/HDL-C indices can predict the mortality of COVID-19. Lower levels of HDL-c and LDL-c were also associated with a worse WHO classification, ICU admission and mortality (Parra S *et al*., 2023).

A prospective cohort study was performed on 98 patients with COVID-19 and mild, moderate, and severe pneumonia showed small dense LDL (sdLDL) particles in patients with severe disease. Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) concentrations in COVID-19 patients decreased significantly compared to healthy individuals (Lalosevic M *et al*., 2022). Furthermore, additional studies have reported a relationship between reduced LDL-C and HDL-C levels and the severity of COVID-19 disease (Wei X *et al*., 2020).

It has been reported that on 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). Impaired HDL antioxidant activity further results in lipid oxidation, specifically generating oxidized LDL (oxLDL). oxLDL and oxidized HDL (oxHDL) are potent activators of the oxidized LDL scavenge receptor (LOX-1), inducing further inflammation (Sorokin AV *et al*., 2020).

However, even today the persistent effects on LDL after the termination of inflammation by SARS-CoV-2 remain unexplained. A recent explanation concerns the contribution of two factors that may increase during inflammation, proprotein convertase subtilisin/kexin type 9 (PCSK9) and angiopoietin-like protein 3 (ANGPTL3). PCSK9 has a major effect on hepatic receptor-mediated LDL catabolism and ANGPTL3 regulates the production of LDL from its precursor very low-density lipoprotein (Durrington P, 2023).

CONCLUSION

As studied, metabolic alterations and especially lipoprotein metabolism disorders in patients with COVID-19, may affect the course and outcome of the disease. Consequently, the investigation of the lipid profile of the patients is of primary importance.

In summary, the measurement and analysis of lipid metabolism and blood lipid profiles of patients with COVID-19 should be considered as a clinical tool to assess the health status and prognosis of mortality from SARS-CoV-2.

Consequently, the knowledge of the contribution of lipids to the health status of patients is extremely important in terms of the design and safety of special treatments for COVID-19.

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