LIPID AND LIPOPROTEIN LEVELS IN PATIENTS WITH COVID-19 INFECTIONS

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ABSTRACT

Numerous studies have observed a decrease in total cholesterol, LDL-C, HDL-C, and apolipoprotein B and A-I levels in patients with COVID-19 infections, similar to what is observed with other infections. In most studies the decrease in LDL-C and/or HDL-C was more profound the greater the severity of the illness. LDL-C and HDL-C levels were inversely correlated with C-reactive protein (CRP) levels i.e., the lower the LDL-C or HDL-C level the higher the CRP levels. Patients with low HDL-C and/or LDL-C levels at admission to the hospital were at an increased risk of developing severe disease compared to patients with high levels. With recovery from COVID-19 infections the serum lipid levels return towards levels present prior to infection. In patients that failed to survive, total cholesterol, LDL-C, and HDL-C levels were lower at admission to the hospital and continued to decline during the hospitalization. In patients with COVID-19 infections the serum triglyceride levels were variable. Lipoprotein (a) levels increase during COVID-19 infections. Several studies using the UK Biobank and other databases have shown that low HDL-C and apolipoprotein A-I levels measured many years prior to COVID-19 infections were associated with an increased risk of COVID-19 infections and death from infection while LDL-C, apolipoprotein B, lipoprotein (a), and triglyceride levels were not consistently found to be significantly associated with an increased risk. A 10 mg/dl increase in HDL-C or apolipoprotein A1 levels was associated with ~10% reduced risk of COVID-19 infection. It should be noted that these observations are subject to the caveats of confounding variables and reverse causation effecting the results. Several studies have found that homozygosity for apolipoprotein E4/4 is associated with a 2-3- fold increased risk of COVID-19 infections and this increase was not due to dementia or Alzheimer's disease. During the COVID-19 pandemic, diet, exercise, and lipid lowering therapy should be continued. For those who become symptomatic, lipid lowering therapy, if feasible, should also be continued throughout the duration of the illness. Individuals who are naïve to treatment but for whom lipid lowering therapy is indicated should be started on treatment. Whether lipid lowering drugs have beneficial effects when given prior to or during COVID-19 infections is uncertain but randomized controlled studies are in progress. In patients with severe symptoms of COVID-19 who are too ill to take oral medications, lipid lowering medications may be temporarily suspended. Medications should be re-started when the patient has recovered and able to take oral medications. One needs to be aware that

certain drugs that are used to treat COVID-19 infections may interact with lipid lowering drugs. Remdesivir and Paxlovid (nirmatrelvir and ritonavir) are metabolized by the Cyp3A4 pathway and statins that are also metabolized by this pathway should be avoided (atorvastatin, simvastatin, and lovastatin). Because drug therapy for patients with COVID-19 infections is rapidly evolving one needs to be alert for potential drug interactions.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has resulted in a world-wide pandemic. The infection is spread through large respiratory droplets and fine respiratory aerosols. The majority of COVID-19 infections are either asymptomatic or result in only mild disease but in a substantial proportion of patients the infection leads to a respiratory illness requiring hospital care and respiratory support, which can have a fatal outcome. Older age, male gender, obesity, diabetes, cardiovascular disease, and hypertension are some of the pre-existing factors that increase the risk of severe infection and death. As of March 15, 2022, there have been over 6 million deaths worldwide according to the John Hopkins Corona Virus Resource Center.

LIPID ABNORMALITIES IN PATIENTS WITH COVID-19 INFECTIONS

Background

Patients with a variety of different infections (gram positive bacterial, gram negative bacterial, viral, tuberculosis, parasites) have similar alterations in plasma lipid levels. Specifically, total cholesterol, LDL-C, and HDL-C levels are decreased while plasma triglyceride levels may be elevated or inappropriately normal for the poor nutritional status (1-12). Apolipoprotein A-I, A-II, and B levels are also reduced (1,7,8). HIV, Epstein-Barr virus, and Dengue fever are viral infections that demonstrate these lipid alterations (13-15). The alterations in lipids correlate with the severity of the underlying infection i.e., the more severe the infection the more severe the alterations in lipid and lipoprotein levels (16-18). During recovery from the infection plasma lipid and lipoprotein abnormalities return towards levels present prior to infection. Of note studies have demonstrated that the degree of reduction in total cholesterol, LDL-C, HDL-C, and apolipoprotein A-I are predictive of mortality in patients with severe sepsis (19-26).

Studies in Patients with COVID-19

Numerous studies have reported a decrease in total cholesterol, LDL-C, HDL-C, apolipoprotein A-I, and apolipoprotein B levels and variable changes in triglycerides in patients with COVID 19 infections (27-43). An NMR analysis in patients with severe COVID-19 infections revealed a decrease in HDL particles particularly low numbers of small HDL particles and a predominance of small LDL particles compared to larger LDL particles (44). In addition to a decrease in HDL levels changes in HDL protein concentrations occur with decreased apolipoprotein A-I, apolipoprotein A-II, pulmonary surfactant-associated protein B, and paraoxonase and increased serum amyloid A and alpha-1 antitrypsin (34,45). With recovery from the acute COVID-19 infection lipid levels return towards levels present prior to infection (27-29,46,47). LDL-C and HDL-C levels were inversely correlated with C-reactive protein (CRP) levels i.e., the lower the LDL-C or HDL-C level the higher the CRP levels (27,28,31,48,49). The lower the HDL-C and LDL-C levels the greater the severity of the COVID-19 infection (28,30-33,36-38,41,47,48,50). Low LDL-C and/or HDL-C levels at

admission to the hospital predicted an increased risk of developing severe disease and mortality and in these very ill patients, lipid levels declined during the hospitalization (27,37,38,40,46,48,50,51). In a meta-analysis of 19 studies and a meta-analysis of 22 studies decreased levels of total cholesterol, HDL-C, and LDL-C was associated with severity and mortality in COVID-19 patients (52,53).

In patients with COVID-19 infections serum triglyceride levels were variable. This is likely due to the decreased food intake that commonly occurs in ill patients resulting in a decrease in triglyceride levels. Additionally, the timing of when blood samples were obtained, the use of medications that may affect triglyceride levels (for example glucocorticoids or propofol), or the development of disorders that effect triglyceride levels (for example poorly controlled diabetes) could have confounded the triglyceride results. Severe hypertriglyceridemia (triglycerides > 500mg/dL) occurred in 33.3% of patients with COVID-19 associated acute respiratory distress syndrome treated with propofol compared to only 4.3% of patients with non-COVID-19 acute respiratory distress treated with propofol (54). Of note it has been reported that serum triglyceride levels were elevated in patients with mild or severe infections but not in patients with critical illness (respiratory or multiple organ failure and septic shock) (31). In contrast, a study reported that triglyceride levels were higher in patients that died from COVID-19 compared to patients that were critically ill or non-critically ill (50). In another study a severe outcome was associated with lower HDL-C levels and higher triglyceride levels (55). However, a meta-analysis did not find that triglyceride levels were associated with disease severity in patients with COVID-19 (53). NMR analysis in patients with severe COVID-19 infections revealed an increase in triglyceride rich lipoprotein particles primarily due to an increase in the small and very small subfractions (44). Finally, a patient with a mild COVID-19 infection has been reported to develop marked hypertriglyceridemia due to transient inhibition of lipoprotein lipase activity presumably due to the development of autoantibodies against lipoprotein lipase similar to what has been reported in patients with autoimmune disorders such as systemic lupus erythematosus (56).

Lipoprotein (a) levels increase during COVID-19 and appear to be associated with an increased risk of venous thromboembolism (57). It had been hypothesized that an increase in Lp(a) could contribute to some of the clinical abnormalities, such as thrombosis, seen during severe COVID-19 infections and these results support that hypothesis (58).

The potential mechanisms by which infections and inflammation alter lipid and lipoprotein levels and the consequences of these alterations are discussed in the Endotext chapter entitled “The Effect of Inflammation and Infection on Lipids and Lipoproteins” (59).

Table 1. Effect of COVID-19 Infection on Lipid and Lipoprotein Levels
Triglycerides- Variable but tend to be increased
Total cholesterol- Decreased
HDL-C- Decreased

LDL-C- Decreased
Small dense LDL- Increased
Lp(a)- Increased
Apolipoprotein A-I- Decreased
Apolipoprotein B- Decreased

DO PRE-INFECTION LIPID LEVELS PREDISPOSE TO SEVERE COVID-19 INFECTION?

Background

Numerous observational studies have suggested that low LDL-C and/or HDL-C levels increase the risk of developing infections and sepsis (60-72). Of course, it must be recognized that confounding variables could account for this association. For example, unrecognized disease (for example pulmonary or gastrointestinal disorders) could result in decreased HDL-C and LDL-C levels and independently also increase the risk of infections and sepsis.

Studies employing a genetic approach to epidemiology, which reduces the risk of confounding variables and reverse causation, have been used to investigate the relationship of lipid levels with the risk of infections and sepsis. In a study by Madsen and colleagues using two common variants in the genes encoding hepatic lipase and cholesteryl ester transfer protein that regulate HDL-C levels found in 97,166 individuals from the Copenhagen General Population Study that low HDL-C levels increased the risk of infection supporting the observational studies that low HDL-C levels increase the risk of infection (66). In studies by Walley and colleagues HMGCoA reductase and PCSK9 genetic variants that decrease LDL-C levels genetically were not associated with an increased mortality from sepsis suggesting that the observational studies linking low LDL-C with sepsis may have been due to confounding variables (70). In support of this contention a study demonstrated that low LDL-C levels were significantly associated with increased risk of sepsis and admission to intensive care unit, however, this association was found to be due to comorbidities (73). Finally, Trinder and colleagues using the UK Biobank data base (407,558 individuals) demonstrated that elevated levels of HDL-C and LDL-C were associated with a reduced risk of infectious disease related hospitalizations similar to prior observational studies while elevated levels of triglycerides were associated with increased risk of infectious disease related hospitalizations (74). However, this study also employed a genetic approach and found that for genetically determined lipid levels, only increased HDL-C levels were significantly associated with a reduced risk of hospitalizations for infectious disease and mortality from sepsis suggesting that HDL could be causally related to infections (74). Taken together these studies demonstrate that low LDL-C levels that are associated with an increased risk of infections are not likely to be a causal association while the low HDL-C levels that are associated with an increased risk of infection appears to be causal.

This protective effect of HDL could be due to HDL particles binding lipopolysaccharide and lipoteichoic acid, compounds that mediate the excessive immune activation in sepsis or to the immunomodulatory, antithrombotic, and antioxidant properties of HDL (6,75). Additionally, HDL may have direct effects on

viruses that decrease their infectivity by direct viral inactivation, interference with viral entry into the cell, or inhibition of virus-induced cell fusion (76-79). Finally, HDL has an antiviral effect against SARS-CoV-2 (COVID-19) (80).

COVID-19 Infections

Several studies using the UK Biobank and other databases have shown that elevated HDL-C and apolipoprotein AI levels measured many years prior to COVID-19 infections were associated with a reduced risk of COVID-19 infections while LDL-C, Apo B, lipoprotein (a) and triglyceride levels were not consistently found to be significantly associated with an increased risk (81-89). Hilser and colleagues found that a 10 mg/dl increase in HDL-C or apolipoprotein A1 levels were associated with ~10% reduced risk of COVID-19 infection (82). In addition, an increased risk of death from COVID-19 infections was also inversely related to HDL-C and apolipoprotein A1 levels (82). Thus, there is consistent evidence that HDL-C and apolipoprotein A1 levels measured many years prior to COVID-19 play a role in determining the risk of developing COVID-19 infections. It should be noted that these were not genetic based analysis so these observations, as discussed above, are subject to the caveats of confounding variables and reverse causation effecting the results.

Aung et al reported that genetically higher exposure to LDL-C was related to increased risk of COVID-19 (84) and Zhang and colleagues reported that genetically determined higher total cholesterol and apolipoprotein B levels might increase susceptibility for COVID-19 (90). However, other studies found no evidence supporting an association of genetically induced increases in LDL-C and apolipoprotein B levels with an increased risk for severe COVID-19 infections (82,91-93). Hilser et al was also unable to demonstrate a link between genetically determined HDL-C and triglyceride levels and COVID-19 infection risk (82). Others have also not been able to demonstrate a genetic link of HDL-C, or triglyceride levels with COVID-19 infections (93). However, a Mendelian randomization study found a causal effect of higher serum triglyceride levels on a greater risk of COVID-19 severity (92). Lp(a) genetic risk scores were similar in COVID-19 infected patient and controls (89). Given the variability of results additional studies are required to determine whether LDL-C, apolipoprotein B, apolipoprotein A-I, HDL-C, or triglyceride levels have a causal role in determining the risk or severity of COVID-19 infections.

Several studies have found that homozygosity for apolipoprotein E4/4 is associated with a 2-3- fold increased risk of COVID-19 infections and this increase was not due to dementia or Alzheimer's disease (82,94,95). Interestingly, in patients with HIV, apolipoprotein E4/4 is associated with an accelerated disease progression and death compared with apolipoprotein E3/3 (96). Additionally, individuals who are apolipoprotein E3/4 have an increased inflammatory response to toll receptor ligands compared with patients who are apolipoprotein E3/3 (97). The mechanisms by which apolipoprotein E4/4 increases the risk of COVID 19 infections remains to be elucidated.

LIPID LOWERING DRUGS and COVID-19 INFECTIONS

Detailed information on cholesterol and triglyceride lowering medications is provided in the Endotext chapters entitled “Cholesterol Lowering Drugs” and Triglyceride Lowering Drugs” (98,99). Only information that is of unique importance with regards to lipid lowering drugs and COVID-19 infections will be discussed in this chapter. For a detailed review of

lipid lowering drug therapy in COVID-19 patients see "Managing hyperlipidaemia in patients with COVID-19 and during its pandemic: An expert panel position statement from HEART UK" (100).

Statins

Statins have pleiotropic effects, including decreasing inflammation and oxidative stress, improving endothelial function and immune response, and inhibiting the activation of coagulation cascade, all of which could be beneficial in patients infected with SARS-CoV-2 (101,102). In contrast to these potentially beneficial effects, statins upregulate the ACE2 receptor, the receptor that the SARS-CoV-2 virus uses to enter cells, which could potentially increase the severity of the infection (101,102).

Because of the possibility that statins could have beneficial effects on COVID-19 infections there have been a large number of observational studies comparing the severity of disease and/or mortality in patients taking statins vs. patients not taking stains. Most meta-analyses have found that statins reduce severity of disease and/or mortality (103-108). It should be appreciated that these observation studies have potential flaws and cannot definitively prove that statins are beneficial in COVID-19 infections. In a single randomized trial statin therapy did not reduce disease severity or mortality compared to placebo (109). It is worth noting that a meta-analysis of 7 randomized trials with 1720 patients examining the effect of statins in sepsis (not COVID-19 infections) did not demonstrate any benefit compared to placebo (110). However, the absence of harm from statin therapy in the majority of the COVID-19 observational studies and in the single randomized trial makes it reasonable to continue statin therapy in COVID-19 infected patients for their well-recognized benefits on cardiovascular disease.

One needs to be aware of potential drug interactions with statins and some of the drugs used to treat COVID-19 infections (see table 3) (100). Remdesivir is metabolized by the Cyp3A4 pathway and statins that are also metabolized by this pathway should be avoided (atorvastatin, simvastatin, and lovastatin) (100). With the antiretroviral drug, nirmatrelvir and ritonavir (Paxlovid), it is recommended to avoid statins metabolized by the Cyp3A4 pathway (atorvastatin, simvastatin, and lovastatin) and use low dose rosuvastatin therapy (100). Tocilizumab by inhibiting IL-6 can increase CYP3A4 activity thereby reducing the LDL-C lowering effect of atorvastatin, simvastatin, and lovastatin. Additionally, certain drugs (for example nirmatrelvir and ritonavir) that treat COVID-19 are only used for a short period of time and temporarily stopping statin therapy may be a reasonable approach.

Ezetimibe

A single study reported that patients taking ezetimibe had significantly reduced odds for SARS-CoV-2 hospitalization (OR=0.513, 95% CI 0.375-0.688) (111). The mechanism for this effect is not clear and additional studies are required.

PCSK9 Inhibitors, Evinacumab, and Bempedoic Acid

There is no information with regards to COVID-19 Infections and these cholesterol lowering drugs.

Bile Acid Sequestrants

There is no information with regards to COVID-19 Infections. Because bile acid sequestrants can bind drugs in the GI tract and decrease their absorption, care must be taken when using other oral medications in patients taking bile acid sequestrants.

Fibrates

Fibrates have anti-inflammatory properties (112). In a cohort study fenofibrate did not reduce the severity of COVID-19 infections (113). In patients treated with tocilizumab the use of fibrates should be suspended (100).

Omega-3-Fatty Acids

Omega-3-fatty acids have anti-inflammatory properties (114). In a randomized trial 2 grams per day of Docosahexaenoic acid (DHA) + Eicosapentaenoic acid (EPA) for 2 weeks improved the clinical symptoms of COVID-19 infection and reduced markers of inflammation (C-reactive protein and erythrocyte sedimentation rate) (115). In another randomized trial the administration of 400mg EPA and 200mg DHA per day decreased severity and improved survival in critically ill patients with COVID-19 infection (116). Additional studies are needed to confirm these intriguing results.

Niacin

There is no information with regards to COVID-19 Infections.

Lomitapide

Lomitapide is metabolized in the liver through CYP3A4 and lomitapide is also an inhibitor of CYP3A4 (100). Therefore, one needs to be concerned about potential drug interactions.

Volanesorsen

The major side effect of volanesorsen is thrombocytopenia. Studies have suggested that low platelet levels are associated with an increased risk of severe disease and mortality in patients with COVID-19 infections (100). Therefore, it is recommended that volanesorsen therapy be discontinued in patients infected with COVID-19 until the infection resolves.

Future Studies

There are a large number of on-going randomized trials of the effect of lipid lowering drugs in COVID-19 infections (table 2) (117). For details on these trials see reference (117).

Table 2. On-Going Randomized Trials of Lipid Lowering Drugs

	Number of RCTs	Total Number of Patients
Statins	17	18,215
Fibrates	3	1,050
Niacin	5	1,200
Omega-3 fatty acids	14	21,898

RCTs- randomized controlled trials

Interaction Between Drugs to Treat COVID-19 and Lipid Lowering Drugs

The effect of various drugs that are used to treat COVID-19 infections and lipid lowering drugs are shown in table 3. Because drug therapy for patients with COVID-19 infections is rapidly evolving one needs to be alert for the use of new drugs with potential drug interactions.

Table 3. Interactions Between Drugs to Treat Covid-19 and Lipid Lowering Drugs

Covid-19 Drugs	Drug Interactions
Nirmatrelvir and Ritonavir (Paxlovid)	Contraindicated with drugs that are highly dependent on CYP3A for clearance and thereby increases levels of lovastatin, simvastatin, and atorvastatin. Also increases levels of rosuvastatin by a different mechanism but can use low dose.
Monoclonal antibodies against spike protein	No drug interactions
Remdesivir (Veklury)	Metabolized by the Cyp3A4 pathway and therefore should avoid lovastatin, simvastatin, and atorvastatin.
Molnupiravir (Movfor)	No drug interactions
Baricitinib (Olumiant)	No drug interactions
Tocilizumab (Actemra)	Deceasing IL-6 can upregulate CYP3A and reduce the activity of lovastatin, simvastatin, and atorvastatin.
Glucocorticoids	No drug interactions

MANAGEMENT OF HYPERLIPIDEMIA DURING THE COVID-19 PANDEMIC

During the COVID-19 pandemic diet and exercise should be continued and there is no reason to stop lipid lowering therapy. Patients on lipid lowering therapy should continue to take their medications and patients who have indications for starting lipid lowering therapy should be started on therapy (100). In patients who are asymptomatic or have only mild symptoms of COVID-19 they should also continue their lipid lowering medications (100). This is particular important as studies have shown an association with influenza and other respiratory infections and myocardial infarctions (118-120). In patients with severe symptoms of COVID-19 who are too ill to take oral medications, lipid lowering medications may be temporarily suspended (100). Medications should be re-started when the patient has recovered and is able to take oral medications.

Liver function test abnormalities are frequently observed in patients with severe COVID-19 infections. If the alanine transaminase (ALT) or aspartate transaminase (AST) is greater than 3 times the upper limit of normal lipid lowering therapy should be stopped (100). Creatine kinase measurements should be considered when clinically indicated and in patients who are critically ill. It is recommended that statin therapy be stopped if creatine kinase rises 10-

fold (generally to levels above 2000 IU/L) in asymptomatic patients or at a lower level of 5-fold upper limit of normal in symptomatic patients (100).

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