**LIPID AND LIPOPROTEIN LEVELS IN PATIENTS WITH COVID-19 INFECTIONS**

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**ABSTRACT**

A number of studies have observed a decrease in total cholesterol, LDL-C, and HDL-C levels in patients with COVID-19 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 levels at admission to the hospital were at an increased risk of developing a severe disease compared to patients with high HDL-C 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. In a study using the UK Biobank it was observed that elevated HDL-C and Apo A levels were associated with a reduced risk of testing positive for SARS-CoV-2 while LDL-C, Apo B, and triglyceride levels were not found to be significantly associated with an increased risk. 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. 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 is metabolized by the Cyp3A4 pathway and statins that are also metabolized by this pathway should be avoided (atorvastatin, simvastatin, and lovastatin). With the antiretroviral drugs (lopinavir/ritonavir) it is recommended to use low dose rosuvastatin therapy. Tocilizumab interferes with both the CYP3A4 and CYP2C9 pathways of metabolism and therefore it is recommended to temporarily suspend treatment with statins. 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 contact and 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, obesity, diabetes, cardiovascular disease, and hypertension are some of the pre-existing factors that increase the risk of severe infection and death.

**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 (1-10). HIV and Dengue fever are chronic viral infections that demonstrate these lipid alterations (11,12). 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 (13-15). 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, HDL-C, and apolipoprotein A-I are predictive of mortality in patients with severe sepsis (16-22).

**Studies in Patients with COVID-19**

A number of studies have observed a decrease in total cholesterol, LDL-C, and HDL-C levels in patients with COVID-19 (Table 1).

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| **Table 1. Effect of COVID-19 Infection on Serum Lipid Levels** |
| **Reference** | **Total Cholesterol (mg/dl)** | **LDL-C (mg/dl)** | **HDL-C (mg/dl** | **Triglycerides (mg/dl** |
|  | Control  | COVID | Control | COVID | Control | COVID | Control | COVID |
| (23) | 188 | 152\* | 119 | 85.4\* | 49.5 | 42.1\* | 187 | 102 |
| (24) a | 203 | 137\*\* | 137 | 109\*\* | 54.6 | 42.9\*\*\* | ND | ND |
| (25) | 184 | 169\* | 110 | 88\* | 52 | 49\*\*\* | ND | ND |
| (26) | 181 | 147\*\*\* | 110 | 103\* | 53.4 | 30.4\*\*\* | 106 | 95\* |
| (27)b | - | 125 | - | 70 | - | 27.3 | - | 176 |
| (28) | ND | ND | - | 101 | - | 35.1 | ND | ND |
| (29)c | - | 164 | - | 101 | - | 40.2 | - | 111 |

aControl values in this study are the patient’s pre-infection levels; bICU patients; cpatients with type 2 diabetes; \*P< 0.001; \*\*p< 0.01; \*\*\* p< 0.05.

In most studies the decrease in LDL-C and/or HDL-C was more profound the greater the severity of the illness (Table 2).

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| **Table 2. Effect of Severity of Illness on Lipid Parameters** |
| **Reference** | **Results** |
| (23) | HDL-C was significantly lower in severely ill group compared to moderate group. Total cholesterol, LDL-C, and TG were not different  |
| (25) | HDL-C was decreased significantly in critically ill but not in severely ill patients. LDL-C was significantly decreased in both severely and critically ill patients |
| (30) | HDL-C and LDL-C were lower in patients that died than in critically ill patients and lower in critically ill than non-critically ill patients. |
| (26) | HDL-C were lower in severely ill patients. Total cholesterol, LDL-C, and triglycerides were not significantly different in severely ill patients  |
| (28) | HDL-C were lower in severely ill patients. LDL-C were not significantly different in severely ill patients |
|  (29)\* | HDL-C and LDL-C were decreased in severely ill patients |

\*Patients with type 2 diabetes

Patients with low HDL-C levels at admission to the hospital were at an increased risk of developing a severe disease compared to patients with high HDL-C levels (5). However, in very ill ICU patients neither HDL-C nor LDL-C predicted mortality (6). 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 (23-25). With recovery from COVID-19 infections the serum lipid levels return towards levels present prior to infection (23,24,27). 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 (24,30).

In patients with COVID-19 infections the 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 and the use of medications that may affect triglyceride levels (for example glucocorticoids) could have confounded the triglyceride results. 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) (25). In contrast, another 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 (30).

Data on the effect of COVID-19 infections on lipoprotein(a) (Lp(a)) levels have not yet been reported. It is well recognized that inflammation increases Lp(a) levels so it is likely that COVID-19 infections will also increase Lp(a) (31). It has 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 (32).

The effect of COVID-19 infections in children on lipid levels has not yet been reported.

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” (31).

**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 (33-43). 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, have been used to investigate the relationship of lipid levels with the risk of infections and sepsis. In a study by Madsen and colleagues there seemed to be a reduced risk of infection in those with genetically higher HDL-C levels supporting the observational studies that low HDL-C levels increase the risk of infection (39). In studies by Walley and colleagues genetically lower LDL-C levels 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 (43). In support of this contention a recent study demonstrated that low LDL-C levels were significantly associated with increased risk of sepsis and admission to ICU, however, this association was found to be due to comorbidities (44). Finally, Trinder and colleagues using the UK Biobank data base 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 (45). 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 (45). 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 (46). 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 (47).

**COVID-19 Infections**

In a study by Scalsky and colleagues using the UK Biobank it was observed that elevated HDL-C and Apo A levels were associated with a reduced risk of testing positive for SARS-CoV-2 while LDL-C, Apo B, and triglyceride levels were not found to be significantly associated with an increased risk (48). It should be noted that this was not a genetic based analysis so these observations, as discussed above, are subject to the caveats of confounding variables effecting the results. Ponsford and colleagues using the UK Biobank and HUNT Study (Trøndelag Health Study) data bases reported that there was no evidence supporting an association of genetically induced LDL-C with risk for sepsis or severe COVID-19 infections (49). Thus, while one can hypothesize that low HDL levels increases the susceptibility to COVID-19 infections clearly further studies are required using genetic approaches.

**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” (50,51). 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” (52).

**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 (53,54). 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 (53,54). 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 of these studies demonstrated a reduction in the severity of COVID-19 infections (55-64) but a small number demonstrated either a neutral or harmful effect (65,66). Two meta-analyses have examined the risk of severe illness and/or mortality among statin users compared to non-statin users. A meta-analysis by Kow and Hasan that included four studies with a total of 8,990 COVID-19 patients found that there was a significantly reduced risk for fatal or severe disease with the use of statins (HR=0.70; 95% CI 0.53-0.94) compared to non-use of statins in COVID-19 patients (67). In contrast, a meta-analysis by Hariyanto and Kurniawan that included 9 studies with a total of 3,449 patients failed to demonstrate that statin use reduced the severity of infection or decreased mortality rate from COVID-19 infection (68). It should be appreciated that these observation studies have potential flaws and cannot definitively prove that statins are beneficial in COVID-19 infections. Randomized controlled trials are required and several are reported to be in progress. However, the absence of harm from statin therapy in the majority of these observational studies 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 (52). Remdesivir is metabolized by the Cyp3A4 pathway and statins that are also metabolized by this pathway should be avoided (atorvastatin, simvastatin, and lovastatin) (52). With the antiretroviral drugs (lopinavir/ritonavir) it is recommended to use low dose rosuvastatin therapy (52). Tocilizumab interferes with both the CYP3A4 and CYP2C9 pathways of metabolism and therefore it is recommended to temporarily suspend treatment with statins (52). Dexamethasone does not affect the use of statins. Pitavastatin is minimally metabolized by the cytochrome P450 enzymes and therefore is not subject to as many drug interactions as other statins. Because drug therapy for patients with COVID-19 infections is rapidly evolving one needs to be alert for potential drug interactions.

**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) (62). The mechanism for this effect is not clear and additional studies are required.

**PCSK9 Monoclonal Antibodies 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 (69) but there have not been studies on the effect of these drugs in patients with COVID-19 infections. In patients treated with tocilizumab the use of fibrates should be suspended (52).

**Omega-3-Fatty Acids**

Omega-3-fatty acids have anti-inflammatory properties (70) but there have not been studies on the effect of omega-3-fatty acids in patients with COVID-19 infections.

**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 (52). 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 (52). Therefore, it is recommended that volanesorsen therapy be discontinued in patients infected with COVID-19 until the infection resolves.

**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 (52). In patients who are asymptomatic or have only mild symptoms of COVID-19 should also continue their lipid lowering medications (52). This is particular important as studies have shown an association with influenza and other respiratory infections and myocardial infarctions (71-73). In patients with severe symptoms of COVID-19 who are too ill to take oral medications, lipid lowering medications may be temporarily suspended (52). Medications should be re-started when the patient has recovered and are 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 (52). 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 (52).

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