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The bidirectional interaction of COVID-19 infections and lipoproteins

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COVID-19 infections decrease total cholesterol, LDL-C, HDL-C, and apolipoprotein A-I, A-II, and B levels while triglyceride levels may be increased or inappropriately normal for the poor nutritional status. The degree of reduction in total cholesterol, LDL-C, HDL-C, and apolipoprotein A-I are predictive of mortality. With recovery lipid/lipoprotein levels return towards pre-infection levels and studies have even suggested an increased risk of dyslipidemia post-COVID-19 infection. The potential mechanisms for these changes in lipid and lipoprotein levels are discussed. Decreased HDL-C and apolipoprotein A-I levels measured many years prior to COVID-19 infections are associated with an increased risk of severe COVID-19 infections while LDL-C, apolipoprotein B, Lp (a), and triglyceride levels were not consistently associated with an increased risk. Finally, data suggest that omega-3-fatty acids and PCSK9 inhibitors may reduce the severity of COVID-19 infections. Thus, COVID-19 infections alter lipid/lipoprotein levels and HDL-C levels may affect the risk of developing COVID-19 infections.

The effect of COVID-19 infections on lipids and lipoproteins

During the COVID-19 pandemic, there have been numerous reports of lipid/lipoprotein levels in patients with COVID-19 infections. As seen with other infections, there is a decrease in total cholesterol,

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LDL-C, HDL-C, apolipoprotein A-I (Apo A-I), Apo A-II, and Apo B levels while triglyceride levels have been variable likely due to alterations in food intake in ill patients, the timing of when blood samples were obtained, the use of medications that may affect triglyceride levels (for example glucocorticoids or propofol), and the development of disorders, such as diabetes, that effect triglyceride levels [1–18].

Studies have shown a decrease in HDL particles particularly small HDL particles and a predominance of small LDL particles compared to larger LDL particles [19,20]. Additionally, similar to other infections the composition of HDL is altered during COVID-19 infections with decreased levels of Apo A-I, Apo A-II, pulmonary surfactant-associated protein B, and paraoxonase and increased serum amyloid A and alpha-1 antitrypsin [10,21]. Moreover, cholesterol efflux capacity and the anti-oxidative capacity of apo B-depleted serum were reduced in patients with COVID-19 infections [22].

As seen with other infections recovery from COVID-19 is associated with a return of lipid/lipoprotein levels to baseline values [1–5,23,24]. Interestingly studies have found that months after recovering from COVID-19 infections patients have an increased risk of dyslipidemia with increased total cholesterol, LDL-C, and triglycerides and decreased HDL-C levels [25,26]. Post COVID-19 infection an increased risk of total cholesterol > 5.17 mmol/L (200 mg/dL) (hazard ratio [HR] 1.26, 95% CI 1.22–1.29;), triglycerides > 2.26 mmol/L (150 mg/dL) (HR 1.27, 95% CI 1.23–1.31), LDL-C > 3.36 mmol/L (130 mg/dL) (HR 1.24, 95% CI 1·20–1·29), and HDL-C > 1.03 mmol/L (40 mg/dL) (HR 1.20, 95% CI 1.16–1·25) compared to controls was observed [26]. An increased risk of dyslipidemia was observed in all subgroups based on age, race, sex, obesity, smoking, cardiovascular disease, chronic kidney disease, diabetes, and hypertension. The mechanism accounting for this increased prevalence of dyslipidemia post COVID-19 infection is unknown but perhaps is related to lifestyle changes post illness.

The greater the severity of COVID-19 infections the greater the decrease in total cholesterol, LDL-C, and HDL-C levels [4,6–9,15,18,24,27–30]. High C-reactive protein (CRP) levels, a marker of immune activation, are associated with lower LDL-C and HDL-C levels [1–4,8,29,31]. During COVID-19 infections low levels of total cholesterol, HDL-C, and LDL-C were associated with severity and mortality and low LDL-C and/or HDL-C levels at admission to the hospital predicted an increased risk of developing severe disease and mortality [1–3,14,15,23,27–29,32–34]. Two meta-analyses did not find that triglyceride levels were associated with disease severity in patients with COVID-19 [30,32].

Lp(a) levels are predominantly genetically determined and are very heterogeneous with a 200-fold variation between individuals. In a small study Lp(a) levels were not found to be elevated in patients with COVID-19 infections compared to matched sick controls [35]. However, studies have shown that elevated Lp(a) levels are associated with increased COVID-19 disease severity [35,36]. During hospitalization for COVID-19 infections, Lp(a) levels may increase and this increase has been associated with an increased risk of thrombosis [37]. This increase in Lp(a) is associated with an increase in IL-6 but not C-reactive protein levels [37]. Clearly, additional studies are needed examining Lp(a) levels during COVID-19 infection and their relationship with complications. If a strong link is demonstrated the possibility of lowering Lp(a) levels to reduce the complications of COVID-19 infections could be considered (Table 1).

Mechanisms for the infection-induced changes in lipid and lipoprotein levels

While there is very little information on the mechanisms by which COVID-19 infections alter lipid and lipoprotein levels there are studies on the mechanisms by which other infections alter lipid and lipoprotein levels [38]. Many cytokines, including TNF, IL-1, and IL-6, increase during infections,

Table 1
Lipid and lipoprotein levels during COVID-19 infections.

Total Cholesterol	Decreased
LDL Cholesterol	Decreased
HDL Cholesterol	Decreased
Triglycerides	Variable
Lipoprotein (a)	Uncertain
Apolipoprotein B	Decreased
Apolipoprotein A-I	Decreased

including COVID-19 infections, and the administration of these cytokines mimic the changes in lipid/lipoprotein levels that occur during infections [38]. Additionally, the effect of endotoxin (LPS), a model of gram-negative bacterial infections, on lipid/lipoprotein metabolism is not observed in C3H/HeJ (LPS-resistant) mice, whose macrophages do not produce TNF and IL-1 in response to LPS administration suggesting that the changes in lipid/lipoproteins are mediated by cytokines during infection [38]. Presumably, this is also the case for COVID-19 infections.

LDL-C

The mechanism for the decrease in LDL-C during infections is poorly understood. The reason for this lack of insight is that in the usual experimental models (rodents), infections result in an increase in total cholesterol and LDL-C levels whereas in humans a decrease in LDL-C occurs [38]. The reason for this difference between rodents and humans is not understood but perhaps is related to the differences in baseline LDL-C levels. Humans have much higher baseline LDL-C levels than rodents.

Because of the lack of a convenient animal model most of the studies have been carried out in vitro using human hepatoma HepG2 cells. Various cytokines have been shown to decrease cholesterol and Apo B synthesis and secretion by HepG2 cells [39]. In addition, cytokines have been shown to increase LDL receptor activity in human hepatocyte cell lines [38,40,41]. One would expect these in vitro results to lead to a decrease in serum LDL-C levels but whether these changes also occur in vivo during infections in humans is unknown.

PCSK-9 can increase the degradation of LDL receptors and thereby effect the clearance of LDL and LDL-C levels. In a single study PCSK9 levels were not altered in patients with COVID-19 infections suggesting that changes in PCSK9 levels do not account for the decrease in LDL-C levels seen with COVID-19 infections [42].

HDL-C

There are multiple potential mechanisms that could account for a decrease in HDL-C levels during infections (Table 2) [38]. It is likely that the decrease in HDL-C levels during infections is multifactorial and may vary depending on the type of infection, severity of infection, timing of measurements, and host variables.

Triglycerides

There are a number of alterations in metabolism that occur during infections that could lead to an increase in triglyceride levels or maintain “normal” levels despite decreased food intake [38,57,58]. Both an increase in hepatic VLDL production and secretion and a decrease in the clearance of triglyceride-rich lipoproteins may contribute to the increase in triglyceride levels. The increase in hepatic VLDL production and secretion is accounted for by an increase in fatty acids, which stimulates the synthesis of triglycerides resulting in the increased formation and secretion of VLDL [59,60]. The key driving force stimulating the increased formation and secretion of VLDL is an increase in fatty acids due to an increase in hepatic de novo fatty acid synthesis, an increase in adipose tissue lipolysis with the increased transport of fatty acids to the liver, and a decrease in fatty acid oxidation in the liver likely secondary to a

Table 2
Mechanisms for the infection-induced decrease in HDL-C.

Decreases in hepatic Apo A-I production leading to a decrease in HDL particles [43,44]
Formation of SAA rich HDL that are rapidly cleared from the circulation [45,46]
Decreased LCAT leading to a decrease in cholesterol ester accumulation in HDL [47–50]
Increases in endothelial cell lipase and sPLA2-IIA leading to increased HDL catabolism [50–52]
Decreased ABCA1 and ABCG1 leading to decreased cholesterol content of HDL [53–56]
Exchange of HDL cholesterol for VLDL triglyceride leading to an increase in HDL triglyceride that is metabolized resulting in small HDL that are rapidly catabolized [38,57]
Capillary leakage with redistribution from the intravascular to the extravascular compartment

decrease in PPAR alpha [38,60–64]. Together these alterations increase the availability of fatty acids for the synthesis of triglycerides, the formation of VLDL, and the secretion of VLDL.

In addition to stimulating VLDL production numerous cytokines that increase during infections have been shown to decrease lipoprotein lipase activity, the key enzyme that metabolizes triglyceride-rich lipoproteins [38,65]. Additionally, inflammation also increases angiopoietin-like protein 4, an inhibitor of lipoprotein lipase activity, which would further block the metabolism of triglyceride rich lipoproteins [66]. Thus, both increased production and decreased clearance may play a role in increasing triglyceride levels.

Lp(a)

The synthesis of Apo (a), a key protein constituent of Lp(a), is increased during sustained inflammation [38,57]. The Apo (a) promoter contains several IL-6 response elements and Il-6 stimulates Apo (a) synthesis [67]. Notably an antibody that inhibits IL-6, tocilizumab, decreases Lp(a) levels [68]. Thus, it is likely that infections that result in prolonged increases in IL-6 lead to elevations in Lp(a) levels.

Epidemiologic evidence that plasma lipid and lipoprotein levels affect the risk of infection

A large number of observational studies have shown that low LDL-C and/or HDL-C levels are associated with an increased risk of infection [1,2,69–81]. For example, the occurrence of infections requiring hospitalization or acquired in the hospital in a large cohort of men and women in the Kaiser Permanente Medical Care Program was increased in individuals with low total cholesterol levels [71]. Similarly, another large cohort study found that low LDL-C levels were associated with higher long-term rates of community-acquired sepsis [72]. As a final example, in patients with end-stage renal disease lower LDL-C and HDL-C levels were associated with a higher risk of death from infection [74].

During the COVID-19 pandemic there have been several studies examining the effect of lipid/lipoprotein levels on the risk of developing COVID-19 infections. Studies using the UK Biobank and other large databases have found that decreased 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 while LDL-C, apolipoprotein B, Lp (a), and triglyceride levels were not consistently associated with an increased risk [1,2,82–91]. For example, a 0.26 mmol/L (10 mg/dL) decrease in HDL-C or 10mg/dL decrease in Apo A-I levels were associated with an approximately 10% increased risk of severe COVID-19 infection [83]. Notably, an increased risk of death from COVID-19 infections was also associated with low HDL-C and Apo A-I levels [83]. The relationship between HDL-C levels and risk of COVID-19 infections is also seen in individuals over age 75, a group at high risk of severe infections [87]. Lipoproteins can bind and neutralize many different viruses [38]. Of particular relevance HDL has an antiviral effect against SARS-CoV-2, the virus that causes COVID-19 infections [92].

Confounding factors or reverse causation could explain the association of low LDL-C and/or HDL-C levels with the risk of developing infections. For example, subclinical pulmonary or gastrointestinal disorders could lead to low HDL-C and LDL-C levels and independently to an increased risk of infection. In fact, in a recent study low LDL-C levels were significantly associated with an increased risk of sepsis and admission to the ICU but this association could be accounted for by comorbidities [93]. Thus, other types of studies are required to demonstrate a causal link between low LDL-C and/or HDL-C and the risk of infections, including COVID-19 infections.

Genetic epidemiologic studies examining the effect of lipid levels and the risk of infection

Employing a genetic approach markedly reduces the influence of confounding variables and reverse causation. In the Copenhagen General Population Study cohort of approximately 100,000 participants using two common variants in the genes encoding hepatic lipase and cholesteryl ester transfer protein that regulate HDL-C levels Madsen and colleagues found that low HDL-C increased the risk of infection [76]. These investigators also found that high HDL-C levels were also associated with an increased risk of infection. In the UK BioBank with over 400,000 participants Trinder and colleagues found that an HDL-C polygenic score indicating low HDL levels increased the risk of hospitalizations for infections and mortality from sepsis while LDL-C and triglyceride polygenic scores were not associated with risk of hospitalization for infections or sepsis-induced mortality [94]. In this study, high HDL-C levels were not associated with an increased risk of infections. Additionally, Trinder et al. using seven different cohorts found that CETP variants that increased HDL levels were associated with a reduced risk of infection while CETP variants that decreased HDL-C levels had an increased risk of infections [95]. Finally, HMGCoA reductase and PCSK9 genetic variants that decrease LDL-C levels were not associated with an increase in mortality because of sepsis [79]. The results of these studies suggest that HDL-C levels may play a causal relationship in the risk of developing severe infections.

Genetic epidemiologic studies examining the effect of lipid levels and the risk of COVID-19 infections

Genetic studies in patients with COVID-19 infections have been inconsistent likely due to the relatively small number of individuals studied. Genetically determined higher LDL-C levels have been reported to increase the risk of COVID-19 infections [85]. Similarly, genetically determined higher total cholesterol and Apo B levels might also increase susceptibility for COVID-19 [96]. In contrast, several other studies did not find an association of genetically induced increases in LDL-C and Apo B levels with an increased risk for COVID-19 infections [83,97–99]. Two studies have failed to demonstrate an association of genetically determined low HDL-C levels with COVID-19 infections [83,99]. With regards to genetically determined triglyceride levels a study reported an increased risk of COVID-19 infections [98] while another study did not find an association of genetically determined triglyceride levels with COVID-19 infections [99]. Genetic risk scores for Lp(a) levels were similar in controls and patients with COVID-19 infections [91]. Clearly, additional studies are required to determine if there is a connection between genetically determined lipid/lipoprotein levels and the risk of developing COVID-19 infections.

While the studies described above do not clearly link genetically determined lipid/lipoprotein levels with COVID-19 infections studies have consistently found that homozygosity for Apo E4/4 is associated with a 2–3-fold increased risk of COVID-19 infections [83,100,101]. Importantly the increased risk of COVID-19 infections was not due to dementia or Alzheimer's disease. Similarly, disease progression and death in patients with HIV are also accelerated in patients that are Apo E4/4 compared to E3/3 [102]. The mechanism linking Apo E4/4 homozygosity with increased risk of infection is unknown.

Effect of lipid-lowering drugs on COVID-19 infections

Many of the common lipid-lowering drugs have pleiotropic effects that could be beneficial during COVID-19 infections. For example, statins decrease inflammation, oxidative stress, and endothelial dysfunction while loss of PCSK9 activity may be beneficial during infections [103,104]. These potential benefits have created interest in determining the effect of lipid-lowering drugs on COVID-19 infections.

Numerous observational studies have found that patients taking statins have a decreased severity of COVID-19 infection and decreased mortality [105–110]. However, three of the 4 published randomized trials did not find a benefit from statin therapy [111–114]. Clearly, additional studies are required and there are numerous randomized trials in progress (Table 3). Notably, there was no toxicity from statin therapy in patients with COVID-19 infections and therefore it is reasonable to continue statin therapy in patients with COVID-19 infections. One should recognize that in patients treated with remdesivir or

Table 3
On-going randomized trials of lipid-lowering drugs.

T	Number of RCTs	Total number of patients
Statins	17	18,215
Fibrates	3	1050
Niacin	5	1200
Omega-3 fatty acids	14	21,898

RCTs- randomized controlled trials
Table with permission from [2] modified from [121].

Paxlovid (nirmatrelvir and ritonavir) because of drug interactions one must avoid treatment with statins metabolized by the CYP3A4 pathway (atorvastatin, simvastatin, and lovastatin) and use low dose rosuvastatin [115].

A recent randomized placebo-controlled trial of evolocumab, a PCSK9 monoclonal antibody, in 60 patients hospitalized for severe COVID-19 found that the risk of death or need for intubation was markedly decreased (23.3% in evolocumab group vs 53.3% in placebo group) [116]. A small randomized single blind study of 30 patients with COVID-19 infection found that 2 g of docosahexaenoic acid [DHA] + eicosapentaenoic acid [EPA]) for 2 weeks reduced some symptoms of infection such as body pain, fatigue, and appetite [117]. A double-blind, randomized study in 128 critically ill patients found that treatment with 400 mg EPA and 200 mg DHA for 14 days resulted in markedly improved survival (21% in EPA/DHA group vs 3% in controls, P = 0.003) [118]. Finally, a randomized open-label trial in 100 ambulatory patients treated with icosapent ethyl (purified EPA) 8 g daily for 3 days followed by 4 g daily for 11 days found that symptoms were improved compared to usual care [119]. The mechanism by which PCSK9 inhibitors and omega-3-fatty acids are beneficial in patients with COVID-19 is unclear.

A randomized trial did not find any benefit from treatment with fenofibrate [120]. There are no randomized trials determining whether ezetimibe, niacin, bile acid sequestrants, bempedoic acid, or inclisiran have beneficial effects during COVID-19 infections. Additional randomized studies of lipid-lowering drugs are underway (Table 3) [121].

Summary

COVID-19 infections markedly alter lipid/lipoprotein levels and the magnitude of these changes is predictive of the severity of disease. Conversely, pre-existing low HDL-C levels increase the risk of severe COVID-19 infections. Thus, there is a bidirectional relationship between COVID-19 infections and lipid/lipoprotein levels.

Practice points

1) In patients with COVID-19 infections low LDL-C and/or HDL-C levels indicate an increased risk of severe disease and higher mortality
2) In patients with COVID-19 infections high Lp(a) levels may be a marker for increased complications, particularly thrombosis
3) Following recovery from COVID-19 infections patients may be at a higher risk of dyslipidemia
4) Decreased HDL-C and apolipoprotein A-I levels prior to COVID-19 infections are associated with an increased risk of COVID-19 infections
5) Lipid-lowering drugs, particularly PCSK9 inhibitors and omega-3-fatty acids, may be beneficial in COVID-19 infections

Research agenda

1) Determine the mechanisms by which COVID-19 infections alter lipid and lipoprotein levels
2) Determine the mechanisms by which HDL might decrease the risk of severe COVID-19 infections
3) Carry out large epidemiological genetic studies to determine if lipid levels play a causal role in COVID-19 infections
4) Determine the relationship between Lp(a) levels and severity of COVID-19 infections and whether lowering Lp(a) levels during COVID-19 infections is beneficial
5) Determine if lipid-lowering drugs alter the clinical course of COVID-19 infections

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