Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Covid and cholesterol (C&C): Something to worry about or much ado about nothing?

As the world is grappling with the COVID-19 disease 2019 (COVID-19) pandemic, research is ongoing to assess the effect of COVID-19 on various organs of the body and delineate the factors correlating with the severity and outcomes. Hyperlipidaemia, characterized by an increase in one or more of the plasma lipids (triglycerides (TG), total cholesterol(TC), cholesterol esters, phospholipids) or plasma lipoproteins (very low-density lipoprotein (VLDL), low-density lipoprotein (LDL)) along with reduced high-density lipoprotein levels (HDL), has been postulated as a possible exacerbating factor indicating poor outcomes by dysregulating protective immunity and promoting exaggerated pulmonary and systemic inflammatory responses [1].

COVID-19 is an RNA virus having a lipid envelope. Hence, cholesterol biosynthesis pathways play an important role in the assembly, replication and infectivity of these viral particles [2]. Cholesterol-modifying drugs, mainly statins, have been hypothesized to have antiviral effects. These drugs decrease the synthesis, systemic absorption of cholesterol or exhibit direct antiviral activity altering the target cell membrane cholesterol. Statins also have additional non−lipid-related pleiotropic effects. This includes improved endothelial function, atherosclerotic plaques stabilization, anti-inflammatory, immunomodulatory and antithrombotic effects [3,4]. These additional properties of statins might confer a possible benefit in patients infected with COVID-19.

Radenkovic et al. [1] recommended that patients already on statins should continue taking it if diagnosed COVID positive. In high-risk patients having severe COVID-19 disease, statin therapy may be initiated to prevent life-threatening cardiovascular complications. The major reason for discontinuation of statin therapy is statin-associated muscle symptoms. Statin therapy needs to be discontinued in skeletal muscle symptoms and elevated liver enzymes [3].

LDL contributes to vasculopathy in patients with COVID-19. The virus invades the endothelial cells (EC) and causes acute endothelial injury and triggers coagulopathies as significant clinical sequelae. The ECs within atherosclerotic plaques are more vulnerable to an attack from COVID-19 or inflammatory storms, causing a rupture of plaques and a high risk of developing coagulopathy in patients with associated cardiovascular preconditions. Cao et al. suggested that hyperlipidaemia is a significant contributor to endothelial dysfunction leading to atherosclerosis. They recommended lowering LDL levels using statins to ameliorate the degree of vasculopathy and protect the endothelial integrity from COVID-19 attack [5].

However, Wei et al. [6], in their retrospective study, assessed the serum levels of LDL, HDL, and TC in 597 COVID-19 patients and found significantly lower levels of LDL and TC as compared with normal subjects. They also observed that HDL levels decreased significantly only in critical cases as compared to the levels in mild and severe cases. They postulated several mechanisms for this including decreased LDL biosynthesis due to liver dysfunction, altered lipid metabolism due to acute inflammation, elevated free radicals causing lipid degradation and altered vascular permeability causing a leakage of cholesterol molecules into tissues.

Hu et al. [7], observed a similar trend with sharply decreased total cholesterol (TC), HDL and LDL levels. They also observed that HDL level was significantly lower in the patients with COVID-19 primary infection than secondary infection patients. HDL is an anti-inflammatory lipoprotein with protective effects against oxidized lipids. Due to this, they speculated that serum HDL-cholesterol was involved in the regulation of immune cells during COVID-19 infection, which might lead to the significantly dropped HDL-cholesterol level in the patients.

Zhu et al. [8] analysed the blood lipid profile and predictive values in 142 patients with COVID-19 ranging from healthy controls to severely affected (17 cases). They corroborated the findings where TC, HDL, LDL and apolipoprotein A1 (ApoA1) gradually decreased across healthy controls, non-severe group, and severe group. They recognised ApoA1 as an independent risk factor for COVID-19 severity.

Fan et al. [9] analysed the serum lipid levels of 21 patients before they were infected by COVID-19 and during their entire courses of the disease. They observed that the LDL and TC levels in all patients showed significant decreases at the time on admission as compared to the levels prior to infection, remained relatively low during the treatment and returned to the levels prior to infection in patients that survived by the time of discharge. The HDL levels also showed significant decreases at the time on admission as compared to levels prior to recovery. The LDL, HDL and TC levels of the deceased patients ($n = 4$) decreased continuously until death with the LDL levels showing an irreversible decrease.

Sorokin et al. [10] observed a similar trend of lipid changes in their 40 year old male COVID-19 patient with history of cardiovascular disease, not on statin therapy. The TC levels decreased to 50% associated with reductions in HDL and LDL after an acute onset of COVID-19. Changes in lipid levels paralleled the increase in C-reactive protein (CRP). The patient's condition improved drastically after treatment with mechanical ventilation and supportive therapy. The TC returned to preadmission values after about 60 days at the time of discharge.

Ravnskov has stressed through his research work on statins that statin treatment should be stopped in patients with severe COVID-19 infection. Also, more than 20% of statin-treated people suffer

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from serious side effects [11]. Goldstein et al., stated that statins might promote the activation of the inflammatory pathway resulting in increased levels of interleukin-18. This may result in severe pneumonia, ARDS and death in the setting of COVID-19, particularly in older individuals who are more likely to be taking these drugs [12]. Several large randomized trials which tested the addition of statins for ARDS due to non-covid pathologies exhibited no overall benefit or capacity to combat rising levels of IL-18. This suggests that statins when started in the advanced stages of COVID-19, are unlikely to exert useful anti-inflammatory activity [4].

Ray et al. in a review, have concluded that COVID-19 patients already receiving statins for an underlying co-morbid condition, should continue taking it unless there are specific contraindications. De-novo use of statins with no underlying co-morbidity should be weighed by the beneficial effect of statins due to MYD88 antagonism and the risk of low serum LDL cholesterol in increasing severity of COVID-19 infection [13].

In the light of the data supporting hypolipidemia, where the use of statins remains a dilemma, it is prudent to look for other therapies to correct the dyslipidaemia in patients with COVID-19. Bojkova et al. studied the proteomics of infected host cells to look for potential therapy targets and observed that COVID-19 reshapes central cellular pathways such as translation, splicing, carbon metabolism, protein homeostasis and nucleic acid metabolism. Changes were also observed in the proteins involved in lipid and cholesterol metabolism which reside in the endoplasmic reticulum. They inferred that spliceosome and glycolysis inhibitors are potential therapeutic agents for the treatment of COVID-19 [14].

Buschard has recommended using fibrates as a therapy for COVID-19 as it helps in increasing the amount of sulfatide which can decrease the disease severity [15]. Fibrates decrease triglyceride levels and increase HDL levels by targeting fatty acid synthesis and increasing lipoprotein lipase activity. Another interventional trial is ongoing regarding the use of fenofibrate as a metabolic intervention for COVID-19 (FERMIN trial) [16].

Shen et al. [17] performed proteomic and metabolic profiling of sera from 46 COVID-19 patients including 28 severe patients and observed the downregulation of multiple apolipoproteins including APOA1, APOA2, APOH, APOL1, APOD, and APOM. Decrease of APOA1 in serum has been reported during the transition of COVID-19 patients from mild to severe illness [18]. This decrease was more pronounced with severe disease for all lipoproteins. Decreased levels of sphingolipids and glycerophospholipids was observed as well in both non-severe and severe COVID-19 patients [17]. Persistent inflammation leads to decreases in ApoA-1, ApoE thereby adversely affecting the anti-inflammatory, antioxidant, and immunomodulatory function of HDL. Sorokin et al. [10] have asserted that deficits in ApoE function in COVID-19 dyslipidaemia may contribute to disease progression and complications. ApoE is expressed in lung macrophages and the alveolar epithelial cells which can be the mediator of lung inflammation.

Therefore, interventions to improve HDL functionality may be effective for the management of COVID-19 related complications. Pharmacotherapy for increasing ApoA-1 levels or using neutralizing antibodies for blocking the scavenger receptors might prove beneficial in restoring lipoprotein function for the treatment of COVID-19. The rise in eicosanoids and hypercoagulation that occurs in COVID-19 may possibly controlled by combined therapy with omega-3 fatty acids and aspirin [10]. Szabo et al. have stressed upon the supplementation of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in COVID-19 patients as both a supportive therapy and a prevention strategy as it appears to have a potential beneficial effect in managing the cytokine storm [19].

Further studies with human trials are required to fully understand the impact of altered lipid metabolism and cholesterol-modifying drugs on the clinical course of COVID-19 infection. Also, the timing of therapy in the course of the disease for an effective treatment needs to be investigated.

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