Annals of R.S.C.B., ISSN: 1583-6258, Vol. 24, Issue 2, 2020, Pages.1170-1179
Received 24 October 2020; Accepted 15 December 2020

Quick Review on Correlation of COVID- 19 and cholesterol

Dr Versha Prasad

University Institute of Health Sciences, C.S.J.M. University Kanpur

Abstract

This pandemic not only adversely affected the physical health of individuals, but also brought forth significant changes in their lifestyle. India has a widely recognized health care delivery system but due to the lack of organized infrastructure, there is a growing sense of crisis, as the majority (66.53%) of its population reside in rural areas which are plagued with wide discrepancies related to the delivery of health care needs. Infectious diseases are usually associated with low HDL cholesterol (HDL-C) concentrations and sometimes with low LDL cholesterol (LDL-C) concentrations, while triglyceride levels are typically maintained or even increased. Although several mechanisms for the acute fall in cholesterol were suggested, it still remains unclear whether these changes in serum cholesterol are related to viral–host cell fusion and entry , thus, the timing of cholesterol lowering may be fundamental in the management of critically unwell patients, and these therapies might be better suited earlier in the disease course prior to critical care admission. Further investigation is needed on the role of cholesterol and use of statins amongst patients with COVID-19 infections. The safety and availability of statins makes it worthwhile to consider whether such host-response modulating drugs may promote a milder clinical infection if initiated early in the disease process. We also should keep in mind the possible occurrence of muscle symptoms during the course of COVID-19. While myalgias are easily attributable to SARS-CoV-2 infection in statin untreated patients, their differential diagnosis may be cumbersome in COVID-19 patients receiving statins. 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.

Keywords : COVID-19; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Total cholesterol; high-density lipoprotein (HDL)-cholesterol; high-density lipoprotein (HDL)-cholesterol; triglycerides; lipid raft.

1. Introduction

Coronavirus disease (COVID-19), which originated in the Wuhan province of China, was declared as a global pandemic by the World Health Organization (W.H.O) on March 11, 2020.[1] Since then it has spread beyond borders and affected the lifestyle behaviour of people.

This pandemic not only adversely affected the physical health of individuals, but also brought forth significant changes in their lifestyle. India has a widely recognized health care delivery system but due to the lack of organized infrastructure, there is a growing sense of crisis, as the majority (66.53%) of its population reside in rural areas which are plagued with wide discrepancies related to the delivery of health care needs.[2] Needless to say, this pandemic has magnified this dearth by diverting its focus on specific medical conditions, neglecting other issues related to lifestyle behaviour.

The COVID-19 pandemic has rapidly spread worldwide, and it appears to be far from being controlled. While the main pathophysiological mechanisms are being revealed, only some of the factors determining whether some patients have an asymptomatic course while others die

have been identified. Given the limited treatment options, the identification of risk factors related to severe COVID-19 is of paramount importance to improve the prognosis. Age, sex, background therapies and comorbidities are the main clinical determinants of severity.[3,4] High blood pressure and dysglycaemia are associated with a worse prognosis; however, although dyslipidaemia is one of the main cardiovascular risk factors, the association between baseline lipid levels and the prognosis has been less frequently studied. In this respect, a recent umbrella review of systematic reviews suggested that dyslipidaemia may play a role in the severity of SARS-CoV-2 infection.[4]

The SARS-Cov-2 spike protein mediates the entrance of the virus into host cells via surface angiotensin-converting enzyme 2 (ACE2).[5] Host protease transmembrane, serine protease 2 (TMPRSS2) promotes SARS-CoV-2 entry into target cells, which are thought to be host determinants for viral infection in the initial stage. COVID-19 patients may be asymptomatic or symptomatic. The time from exposure to onset of symptoms is about 5.1 days.[6] Pathologically, almost every vital organ in the body, including the lungs, heart, liver, kidneys, eyes, blood vessels, intestines, and brain, can be injured by SARS-CoV-2, leading to devastating consequences

Lipids are crucial in the infection process, as they are important structural components of cellular and subcellular organellar membranes. Membrane lipid components participate in the regulation of transmembrane molecular trafficking, including infectious materials such as viruses. Viral internalization requires the attachment of the virus to the host cell membrane, activating an endocytosis mechanism.[7] The newly synthesized viral particles exit the cells again by crossing the lipid-rich cell membrane. Based on studies of animal models, intracellular cholesterol may increase cellular SARS-CoV-2 infectivity.[8]

Patients with metabolic-associated preconditions are susceptible to SARS-CoV-2 attack and are likely to experience more pronounced symptoms. One pathogenic cofactor associated with hypertension, obesity, diabetes mellitus, and cardiovascular disorders is hypercholesterolemia. We and others have recently reported hypolipidemia in hospitalized COVID-19 patients.[9,10,11] An association between decreases in lipid levels and the severity of the symptoms in patients has been revealed.[9,10,11] Furthermore, emerging evidence has shown that SARS-CoV-2 has a direct impact on the downregulation of lipid-metabolism-related proteins and pathways, leading to dyslipidemia.[12]

In addition to structural and energy supply functions, intracellular lipids also act as intracellular signalling molecules or transcription factors. Viral particles also interfere with these pathways, altering cell physiology and leading to apoptosis and cell death.[13]

Viral Disease Association with Cholesterol

Infectious diseases are usually associated with low HDL cholesterol (HDL-C) concentrations and sometimes with low LDL cholesterol (LDL-C) concentrations, while triglyceride levels are typically maintained or even increased.[14,15] Low HDL-C levels have been proposed as a risk biomarker for different infections.[16] Regarding the SARS-CoV-2 infection, low LDL-C, HDL-C and triglyceride (TG) levels have been described to be associated with an increasing

infection severity, and a role for these lipids in immune mechanisms has been suggested.[13] Low lipid levels during the infection have been associated with the severity of COVID-19.[14] Meanwhile, low plasma lipid concentrations are regarded as a consequence of the hypermetabolic state and undernutrition in the infected patient; however, many metabolic pathways associated with the immune response and infection itself participate in these alterations.[11] Cytokines, inflammatory mediators, modified lipids and intermediate lipid classes generated during the infection interfere with several steps of lipid metabolism by reducing cholesterol synthesis and absorption, decreasing triglyceride-rich lipoprotein clearance or reducing apolipoprotein (apo) A1 synthesis.

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. 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. These additional properties of statins might confer a possible benefit in patients infected with COVID-19.

Radenkovic et al. 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.[17]

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.[18]

However, Wei et al., 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.[19] 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., 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.[20] 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. analysed the blood lipid profile and predictive values in 142 patients with COVID-19 ranging from healthy controls to severely affected (17 cases).[21] They corroborated the findings where TC, HDL, LDL and Apo lipoprotein 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. 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.[22] 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. 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.[23] 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.

Use of Statins in Human Viral Infections

Although there has been almost no evidence on the use of statins in patients with SARS-CoV-2, these drugs have previously been investigated in the treatment of other acute respiratory viral infections such as influenza.[24,25]A study of 1055 adult patients with viral pneumonia found lower rates of mortality and intubation with continued use of statins throughout the hospital stay (odds ratio (OR) 0.26; 95% confidence interval (CI): 0.08–0.81). Similar to SARS-CoV, hepatitis C viral (HCV) replication is closely associated with lipid metabolism, and statins are expected to disrupt this mechanism.[26] Statin treatment in chronic HCV was shown to increase the clearance of the virus from the blood, down-regulate HCV replication , and resulted in clinical reduction in hepatocellular carcinoma.[27,28] Additionally, a meta-analysis by Chopra et al. showed that statin use was associated with lower mortality after pneumonia (OR 0.62, 95% CI: 0.54–0.71) [.

Although several mechanisms for the acute fall in cholesterol were suggested, it still remains unclear whether these changes in serum cholesterol are related to viral–host cell fusion and entry , thus, the timing of cholesterol lowering may be fundamental in the management of critically unwell patients, and these therapies might be better suited earlier in the disease course prior to critical care admission.[29] Lastly, a recent in silico analysis showed that several statins

could serve as potential SARS-CoV-2 main protease inhibitors, with pitavastatin, a highly lipophilic molecule, exhibiting the strongest binding .[30] There are also some reports suggesting that statins might enhance ACE2, which might mitigate the invasion of SARS-CoV-2 through the ACE2 receptor.[31] All these results seem encouraging but need to be confirmed in further observational and interventional clinical studies.

Future Perspective

Further investigation is needed on the role of cholesterol and use of statins amongst patients with COVID-19 infections. The safety and availability of statins makes it worthwhile to consider whether such host-response modulating drugs may promote a milder clinical infection if initiated early in the disease process. We also should keep in mind the possible occurrence of muscle symptoms during the course of COVID-19. While myalgias are easily attributable to SARS-CoV-2 infection in statin untreated patients, their differential diagnosis may be cumbersome in COVID-19 patients receiving statins. Current guidelines for the management of statin intolerance may help to guide clinical decisions, with the recommendation for patients at higher CV risk to continue statin therapy unless absolutely contraindicated.[32] While dealing with COVID-19 patients on statins, we should also take into account drug-to-drug interactions, especially with some macrolides and anti-retroviral therapy, as recently discussed in detail elsewhere.[33]

It is recommended that those patients already on statins should continue with therapy if diagnosed with COVID-19, and adherence should be maintained to a suitable dose, according to the patient's CVD risk. Additionally, based on the above described cholesterol reduction, plaque stabilization, CVD risk prevention, anti-inflammatory, and potential antiviral properties of statins, de novo initiation of statin therapy may be considered in high-risk patients during severe manifestations of COVID-19 to prevent some of the life-threatening cardiovascular complications.

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 from serious side effects.[34] 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.[35] 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.[36]

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.

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.[37]

Shen et al.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.[38,39] 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. Persistent inflammation leads to decreases in ApoA-1, ApoE thereby adversely affecting the anti-inflammatory, antioxidant, and immunomodulatory function of HDL. Sorokin et al.have asserted that deficits in ApoE function in COVID-19 dyslipidaemia may contribute to disease progression and complications.[40] 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 hyper coagulation that occurs in COVID-19 may possibly controlled by combined therapy with omega-3 fatty acids and aspirin .[40]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.[41]

Conclusion

Most conclusions on the interplay between SARS-CoV-2 infection and lipids are based on previous research, carried out on patients with other human coronaviruses infections. For example, it has been reported that lipid rafts may play a fundamental role in coronavirus life cycle . Lipid rafts are microdomains of eukaryote membrane that contain glycosphingolipids, high concentrations of cholesterol, protein of transport and adhesion. The viral infection depends on interactions between components of plasma membrane of host cell and virus envelope. The presence of cholesterol at the surface of target cells is hence essential for enabling coronavirus infections. I ipids, especially cholesterol, may play an important role in viral replication, internalization and immune activation in patients with SARS-CoV-2 infection

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.

References:

1. Radenkovic D., Chawla S., Pirro M., Sahebkar A., Banach M. Multidisciplinary Digital Publishing Institute; 2020. Cholesterol in Relation to COVID-19: Should We Care about it?
2. Baglivo M., Baronio M., Natalini G., Beccari T., Chiurazzi P., Fulcheri E. Natural small molecules as inhibitors of coronavirus lipid-dependent attachment to host cells: a possible strategy for reducing SARS-COV-2 infectivity? *Acta Biomed.* 2020;91:161–164. .
3.Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239–42.
4.Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, Zhong W, Hao P. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. 2020;63(3):457–60.
5.Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565–74. https://doi.org/10.1016/S0140-6736(20)30251-8.**CAS Article PubMed PubMed Central Google Scholar**
6. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. J Virol. 2020;94(7). https://doi.org/10.1128/JVI.00127-20.
7. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG, Lessler J. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020;172(9):577–82. https://doi.org/10.7326/M20-0504.Article PubMed PubMed Central Google Scholar
8 Wei X, Su J, Yang K, Wei J, Wan H, Cao X, Tan W, Wang H. Elevations of serum cancer biomarkers correlate with severity of COVID-19. J Med Virol. 2020;92(10):2036–41. https://doi.org/10.1002/jmv.25957.CAS Article PubMed Google Scholar
9. Fan J, Wang H, Ye G, Cao X, Xu X, Tan W, Zhang Y. Low-density lipoprotein is a potential predictor of poor prognosis in patients with coronavirus disease 2019. Metabolism. 2020:154243.
10. Wei X, Zeng W, Su J, Wan H, Yu X, Cao X, Tan W, Wang H. Hypolipidemia is associated with the severity of COVID-19. J Clin Lipidol. 2020;14(3):297–304. https://doi.org/10.1016/j.jacl.2020.04.008. Article PubMed PubMed Central Google Scholar
11. Hu X, Chen D, Wu L, He G, Ye W. Declined serum high density lipoprotein cholesterol is associated with the severity of COVID-19 infection. Clin Chim Acta.

2020;510:10510. https://doi.org/10.1016/j.cca.2020.07.015.CAS Article PubMed PubMed Central Google Scholar
12. Coronavirus COVID-19 (SARS-CoV-2), Johns Hopkins ABX Guide [https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2].
13. Wiersinga, W. J., Rhodes, A., Cheng, A. C., Peacock, S. J. & Prescott, H. C. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. *JAMA* 324, 782–793 (2020).
14. Abu-Farha, M. *et al.* The role of lipid metabolism in COVID-19 virus infection and as a drug target. *Int. J. Mol. Sci.* 21, 3544–3555 (2020).CAS Article Google Scholar
15. Trinder, M., Boyd, J. H. & Brunham, L. R. Molecular regulation of plasma lipid levels during systemic inflammation and sepsis. *Curr. Opin. Lipidol.* 30, 108–116 (2019).CAS Article Google Scholar
16. Saballs, M. *et al.* HDL-c levels predict the presence of pleural effusion and the clinical outcome of community-acquired pneumonia. *Springerplus* 5, 1491–1500 (2016).CAS Article Google Scholar
17. . Ward N.C., Watts G.F., Eckel R.H. Statin toxicity. *Circ. Res.* 2019;124:328–350. doi: 10.1161/CIRCRESAHA.118.312782. [PubMed] [CrossRef] [Google Scholar]
18. . COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). In., 2020 edn: ArcGIS. Johns Hopkins University; 2020.
19. Wei X., Zeng W., Su J., Wan H., Yu X., Cao X. Hypolipidemia is associated with the severity of COVID-19. *J. Clin. Lipidol.* 2020;14:297–304. doi: 10.1016/j.jacl.2020.04.008. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
20. Hu X., Chen D., Wu L., He G., Ye W. Low serum cholesterol level among patients with COVID-19 infection in Wenzhou, China. *Clin. Chim. Acta.* 2020;10:105–110. doi: 10.1016/j.cca.2020.07.015. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
21. Zhu Zhe, YY, Fan Lingyan. A preliminary study on blood lipid profile in patients with COVID-19. 14 August 2020. PREPRINT (Version 1) available at Research Square. [CrossRef]
22. Fan J., Wang H., Ye G., Cao X., Xu X., Tan W. Letter to the Editor: low-density lipoprotein is a potential predictor of poor prognosis in patients with coronavirus disease 2019. *Metabolism.* 2020;107:154243. doi: 10.1016/j.metabol.2020.154243. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
23. Sorokin A.V., Karathanasis S.K., Yang Z.-H., Freeman L., Kotani K., Remaley A.T. COVID-19—associated dyslipidemia: implications for mechanism of impaired resolution and novel therapeutic approaches. *Faseb. J.* 2020;34:9843–9853. doi: 10.1096/fj.202001451. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
24. Henry C., Zaizafoun M., Stock E., Ghamande S., Arroliga A.C., White H.D. Impact of angiotensin-converting enzyme inhibitors and statins on viral pneumonia. *Proc (Bayl. Univ. Med. Cent.)* 2018;31:419–423. doi: 10.1080/08998280.2018.1499293. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
25. Mehrbod P., Omar A.R., Hair-Bejo M., Haghani A., Ideris A. Mechanisms of action and efficacy of statins against influenza. *Biomed. Res. Int.* 2014;2014:872370. doi: 10.1155/2014/872370. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

26. Fedson D.S. Pandemic influenza: A potential role for statins in treatment and prophylaxis. *Clin. Infect. Dis.* 2006;43:199–205. doi: 10.1086/505116. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
27. Wang C., Gale M., Keller B.C., Huang H., Brown M.S., Goldstein J.L., Ye J. Identification of FBL2 as a geranylgeranylated cellular protein required for hepatitis C virus RNA replication. *Mol. Cell.* 2005;18:425–434. doi: 10.1016/j.molcel.2005.04.004. [PubMed] [CrossRef] [Google Scholar]
28. . Ali N., Allam H., Bader T., May R., Basalingappa K.M., Berry W.L., Chandrakesan P., Qu D., Weygant N., Bronze M.S., et al. Fluvastatin interferes with hepatitis C virus replication via microtubule bundling and a doublecortin-like kinase-mediated mechanism. *PLoS ONE.* 2013;8:e80304. doi: 10.1371/annotation/fcc840e2-225c-4d71-920d-a1eab7747e19. [PMC free article
29. Hu X., Chen D., Wu L., He G., Ye W. Low serum cholesterol level among patients with COVID-19 infection in Wenzhou, China. [(accessed on 21 February 2020)]; doi: 10.2139/ssrn.3544826. Available online: [CrossRef]
30. Reiner Z., Hatamipour M., Banach M., Pirro M., Al-Rasadi K., Jamialahmadi T., Radenkovic D., Montecucco F., Sahebkar A. Statins and the COVID-19 main protease: In silico evidence on direct interaction. *Arch. Med. Sci.* 2020;16:490–496. doi: 10.5114/aoms.2020.94655. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
31. South A.M., Diz D.I., Chappell M.C. COVID-19, ACE2, and the cardiovascular consequences. *Am. J. Physiol. Heart Circ. Physiol.* 2020;318:H1084–H1090. doi: 10.1152/ajpheart.00217.2020. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
32. Nikolic D., Banach M., Chianetta R., Luzzu L.M., Pantea Stoian A., Diaconu C.C., Citarrella R., Montalto G., Rizzo M. An overview of statin-induced myopathy and perspectives for the future. *Expert Opin. Drug Saf.* 2020 doi: 10.1080/14740338.2020.1747431. [PubMed] [CrossRef] [Google Scholar]
33. Banach M., Penson P.E., Fras Z., Vrablik M., Pella D., Reiner Ž., Nabavi S.M., Sahebkar A., Kayikcioglu M., Daccord M. Brief recommendations on the management of adult patients with familial hypercholesterolemia during the COVID-19 pandemic. *Pharmacol. Res.* 2020;158:104891. doi: 10.1016/j.phrs.2020.104891. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
34.Ravnskov U. Cholesterol-lowering treatment may be a major cause of serious Covid-19 infections. *BMJ.* 2020;368 (Published 25 March 2020) [Google Scholar]
35. Goldstein M.R., Poland G.A., Graeber C.W. Are certain drugs associated with enhanced mortality in COVID-19? *QJM: Int. J. Med.* 2020;113:509–510. doi: 10.1093/qjmed/hcaa103. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
36. Schmidt N.M., Wing P.A.C., McKeating J.A., Maini M.K. Oxford Open Immunology; 2020. Cholesterol-modifying Drugs in COVID-19. iqaa001. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
37. . Subir R., Jagat J.M., Kalyan K.G. Pros and cons for use of statins in people with coronavirus disease-19 (COVID-19) *Diabetes Metabol. Syndrome.* 2020;14 doi: 10.1016/j.dsx.2020.07.011. 1225–9. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

38.Shen B., Yi X., Sun Y., Bi X., Du J., Zhang C. Proteomic and metabolomic characterization of COVID-19 patient sera. *Cell.* 2020;182:59–72. doi: 10.1016/j.cell.2020.05.032. e15. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
39. Yang Y., Zhu Z., Fan L., Ye S., Lou K., Hua X. Research Square; 2020. Low Serum Level of Apolipoprotein A1 Is an Indicator of Severity in Patients with Coronavirus Disease 2019. [Google Scholar]
40. Sorokin AV, Karathanasis SK, Yang ZH, Freeman L, Kotani K, Remaley AT. COVID-19-associated dyslipidemia: implications for mechanism of impaired resolution and novel therapeutic approaches. FASEB J. 2020;34(8):9843–53. https://doi.org/10.1096/fj.202001451
41. . Szabó Z., Marosvölgyi T., É Szabó, Bai P., Figler M., Verzár Z. The potential beneficial effect of EPA and DHA supplementation managing cytokine storm in coronavirus disease. *Front. Physiol.* 2020;11:752. doi: 10.3389/fphys.2020.00752. [PMC free article] [PubMed] [CrossRef] [Google Scholar]