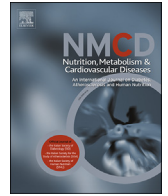




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LETTER TO THE EDITOR

May statins and PCSK9 inhibitors be protective from COVID-19 in familial hypercholesterolemia subjects?



Dear Editor,

Early data from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic disease causing 2019 coronavirus disease (COVID-19) showed that the affected subjects were typically men aged 40–60 years with several comorbidities; in particular, 25% of subjects with COVID-19 treated in an intensive care unit (ICU) had a history of cardiovascular diseases [1]. In this context, young subjects at increased risk of cardiovascular events, such as familial hypercholesterolemia (FH) subjects, may have deleterious consequences due to COVID-19 [2]. Of note, COVID-19 might induce lipid abnormalities, as previously described during Severe acute respiratory syndrome-coronavirus (SARS-CoV) infection [3]; thus, the increased cumulative cholesterol burden might further exacerbate the cardiovascular risk of FH subjects. In this context, the adherence and intensification of lipid lowering therapies is necessary to adequately reduce cardiovascular risk in hypercholesterolemic subjects.

Another aspect to take into consideration is the role of cholesterol during viral infection especially in RNA virus; in fact, it is note that lipids and cholesterol-rich membrane microdomains are essential for flavivirus and coronavirus entries in human cell [4]. Of note, Glende et al. showed that cholesterol-rich membrane microdomains facilitated the interaction between the surface glycoprotein S of SARS-CoV and the cellular receptor angiotensin-converting enzyme 2 (ACE2) [5]. Moreover, after cellular entry, RNA virus require a high amount of intracellular cholesterol and fatty acids for the formation of the replication complex; in particular, Soto-Acosta et al. showed a high amount of cellular cholesterol correlated with an increased activity of the 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) during a RNA virus infection (HMGCR) [6]. In this context, lipid-lowering therapies may have a double beneficial effect in hypercholesterolemic subjects by reducing the cardiovascular risk and interfering with COVID-19.

It is known that statin is the first lipid lowering choice in clinical practice and acts by inhibiting HMGCR.

Interestingly, Panes et al. have previously found that membrane cholesterol is higher in hypercholesterolemic than in normo-cholesterolemic subjects; moreover, they showed that rosuvastatin effectively reduced membrane cholesterol levels in hypercholesterolemic subjects [7]. In this context, it may be interesting to evaluate the impact of high intensity statins (especially hydrophilic statins) in hypercholesterolemic subjects with COVID-19 in terms of morbidity and prognosis.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are the most recently available lipid lowering therapies able to halve low-density lipoprotein (LDL) cholesterol and significantly reduce the cardiovascular risk in hypercholesterolemic subjects such as FH [8]. PCSK9 inhibitors specifically bind and inhibit the circulating protein PCSK9; thus, PCSK9 inhibitors block LDL receptor (LDLR) degradation by PCSK9 and enhance LDLR expression on the hepatocyte surface. Concerning the impact of PCSK9 levels on viral infection, it was shown that PCSK9 promoted the degradation of LDLR-related protein 1 (LRP1) [9]. Of note, Gudleski-O'Regan et al. demonstrated that an increased LRP1 expression was associated with a reduced Cytomegalovirus (CMV) infectivity by depleting intracellular cholesterol in CMV-infected fibroblasts; thus, a higher LRP1 expression may be a defense response to virus infection [10]. Conversely, by inducing LRP1 degradation, PCSK9 might increase viral infectivity and its inhibition could be useful to interfere with the infectivity of several virus such as COVID-19. In line with these considerations, PCSK9 inhibition was not associated with an increased risk of virus infection in clinical trials. It may be interesting to evaluate the impact of PCSK9-inhibitors on morbidity and prognosis of hypercholesterolemic subjects infected by COVID-19.

In conclusion, hypercholesterolemic subjects such as FH have an increased risk of cardiovascular disease and their risk may be worsened by COVID-19; moreover, statins and PCSK9 inhibitors may be useful to reduce the cardiovascular risk and interfere with COVID-19 in FH subjects; further studies are needed to evaluate the impact of these

lipid lowering therapies in hypercholesterolemic subjects infected by COVID-19.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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24 April 2020

Handling Editor: M. Averna