REVIEW ARTICLE

Statins and Covid-19: The Neglected Front of bidirectional effects

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Abstract

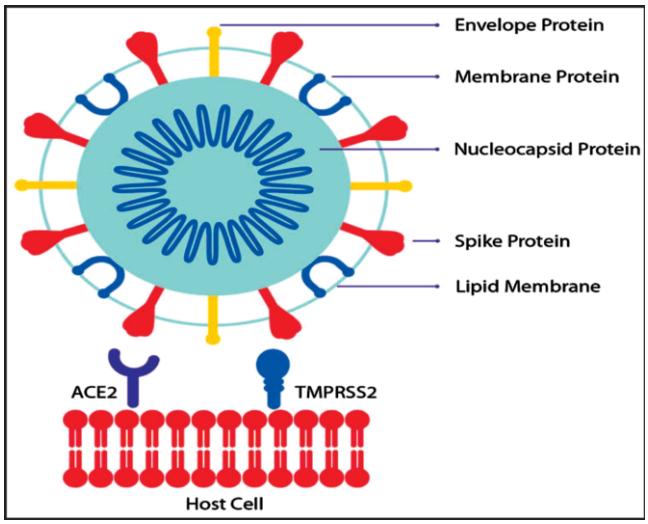
Covid-19 is caused by a novel coronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 binds angiotensin converting enzyme 2 (ACE2), which is greatly expressed in different tissues including lung alveolar type II cells. Infection with SARS-CoV-2 triggers acute host immune response, inflammatory reactions and cytokine storm leading to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Different studies reported the pleiotropic effects of statins such as the anti-inflammatory and immune-modulatory effects via modulation of antigen presentation and adhesion of inflammatory molecules since; statins have potential anti-oxidant and redox balance effects that improve endothelial dysfunction and cardiovascular integrity. Objective of the present study is to verify the beneficial and harmful effects of statins in Covid-19. Statins upregulates ACE2 receptors and attenuates the down-regulation effect of SARS-CoV-2 on the ACE2 receptors. Consequently, reduction of ACE2 receptors augment the deleterious effect of angiotensin II (AngII) which causes vasoconstriction and initiation of ALI. On the other hand, statins therapy may increase risk of viral infections such as SARS-CoV-2 via lowering of low density lipoprotein (LDL) since; circulating LDL adhere and inactivates SARS-CoV-2.

Statin therapy improves the outcomes of Covid-19 pneumonia through anti-inflammatory, immune-modulation, and in vitro anti-SARS-CoV-2 effects. The antiplatelet and antithrombotic effects may reduce Covid-19 induced-coagulopathy and progression of ARDS.

Keywords: SARS-CoV-2, Statins, Covid-19.

Introduction

The present pandemic coronavirus disease 2019 (Covid-19) leads to catastrophic effects worldwide affecting more than 183 million with 4 million confirmed deaths till the fist of July 2021. Covid-19 is caused by a novel coronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] SARS-CoV-2 is a single-strand; RNA virus contains spike protein, enveloped protein and nucleocapside protein similar to that found in other betacoronaviruses like SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV) (Figure-1).[2] SARS-CoV-2 binds angiotensin converting enzyme 2 (ACE2), which is greatly expressed in different tissues including lung alveolar type II cells, proximal renal tubules, heart, and brain. Infection with SARS-CoV-2 triggers acute host immune response, inflammatory reactions and cytokine storm leading to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).[3]



ACE2: Angiotensin converting enzyme 2, TMPRSS2: Transmembrane protease serine 2.

Figure-1: SARS-CoV-2 and host cell entry points.

Different studies reported the pleiotropic effects of statins such as the anti-inflammatory and immune-modulatory effects via modulation of antigen presentation and adhesion of inflammatory molecules since; statins have potential anti-oxidant and redox balance effects that improve endothelial dysfunction and cardiovascular integrity.[4,5] The pleiotropic effects of statins are chiefly mediated through inhibition of isoprenoids production, which are necessary constituents of guanosin triphosphatases (GTPases), which inhibit the transcription of pro-inflammatory mediators'.[6] Therefore, statins have

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been proven to be effective as anti-inflammatory and immune-modulatory agents in different infectious diseases including viral pneumonia and bacterial sepsis.[7] In addition, statins therapy reduces cytokine storm and development of ARDS in avian influenza pneumonia and H1N1 pandemic 2009.[8]

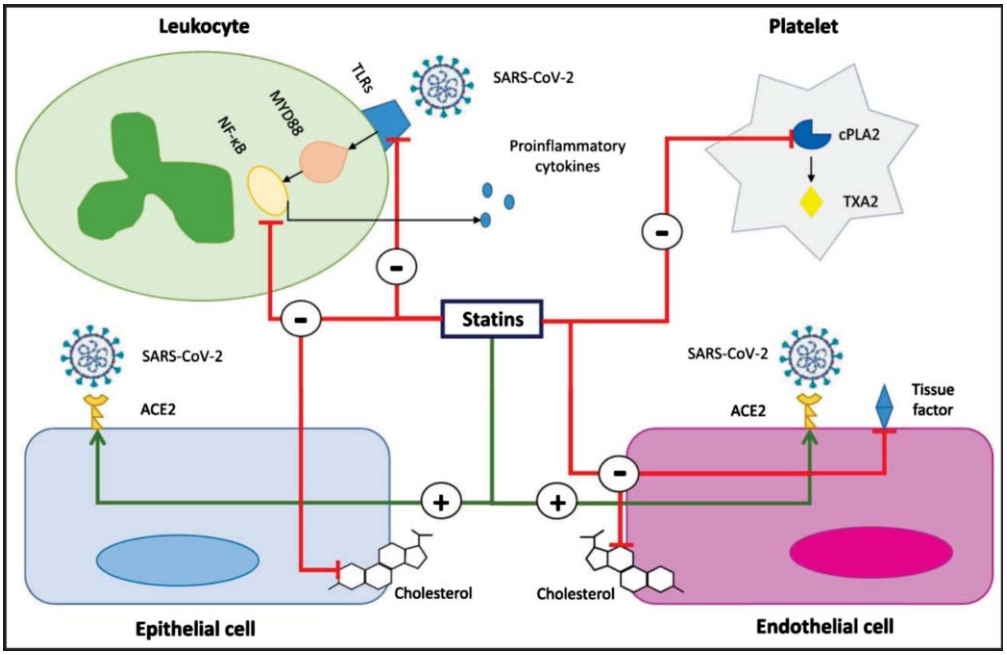
Beneficial effects of statins in Covid-19: It has been reported that both SARS-CoV-1 and SARS-CoV-2 interact with Toll-like receptors (TLRs) on the cell membrane and increase the expression of myeloid differentiation primary response 88 (MYD88) genes, thereby activating pro-inflammatory reaction with development of ALI and ARDS. Statins therapy stabilize MYD88 gene and attenuates pro-inflammatory reactions in Covid-19 induced-ALI (Figure-2).[9]

Moreover, statins upregulates ACE2 receptors and attenuates the down-regulation effect of SARS-CoV-2 on the ACE2 receptors. Consequently, reduction of ACE2 receptors augment the deleterious effect of angiotensin II (AngII) which causes vasoconstriction and initiation of ALI.[10] It has been shown that administration of recombinant ACE2 might be effective in attenuation of ARDS in Covid-19 patients.[11]

Furthermore, statins therapy improve lipid profile with potential cardio-protective effect, thereby prevents cardiovascular complications that are linked with Covid-19 such as heart failure, arrhythmias and myocardial injury.[12] More to the point, an in silico study by Reiner et al found that statins disrupt SARS-CoV-2 viral maturation though binding and inhibition of viral main protease with suppression of glycoprotein processing. Therefore, because statins have potent anti-SARS-CoV-2 and anti-inflammatory qualities, so it may be useful in the management of Covid-19 induced complications.[13]

A retrospective study by Zhang et al in China found that statins therapy was associated with significant reduction in the mortality of Covid-19 in 21 hospitals.[14] Statin therapy also improves the clinical outcomes of Covid-19 patients.[15] It has been revealed that statin therapy reduces endothelial dysfunction and activated thrombo-embolic disorders that are associated with Covid-19 through antiplatelet and modulation through the expression of thrombomodulin.[16] Therefore, because statins prevent coagulopathy in Covid-19 patients as evident by reduction of D-dimer, so it may be used with the standard therapy in treating Covid-19.[17]

Harmful effects of statins in Covid-19: In spite of beneficial effects of statins, different studies reported that statins therapy may increase risk of viral infections such as SARS-CoV-2. Subir et al illustrated that lowering of plasma low density lipoprotein (LDL) by statins may increase the infectivity of SARS-CoV-2 since; circulating LDL adhere and inactivates SARS-CoV-2, thus this finding might explain of low LDL and cholesterol serum levels in patients with Covid-19 pneumonia.[18]



cPLA2: cytosolic phospholipase A2, TXA2: thromboxane A2.

Figure-2: Interactions between SARS-CoV-2 and TLR.

However, the potential mechanism for reduction of cholesterol and LDL is correlated to the viral entry and viral host interaction.[19] Nevertheless, patients on statin therapy should remain on it if they develop Covid-19 and if they have cardiovascular complications.[20,21]

Above and beyond, statins therapy may interfere with host innate immunity during SARS-CoV-2 infection through inhibition of TLR-MYD88 pathway.[22] Similarly, Shrestha et al disclosed that up-regulation of cell

membrane LDL receptors by statins increases receptor-mediated endocytosis of SARS-CoV-2 by formation of lipid draft which is suitable for the entry of enveloped viruses such as SARS-CoV-2.[23] However, Radenkov et al discussed this subject more precisely in particular of cell membrane lipid drafts and their relation in SARS-CoV-2 infection. Lipid drafts are plasma membrane subdomains contain glycosphingolipid and cholesterol, and regarded as entry-point into host cells and improve viral infectivity. In addition, lipid draft intercede the communication between SARS-CoV-2 and ACE2 and facilitates viral endocytosis.[24] Moreover, lipid draft also contains other viral entry-point such as clathrins, caveolins and dynamin thus; depletion of lipid draft cholesterol may reduce viral mRNA.[25] A recent meta-analysis illustrated that no noteworthy reductions was observed in either Covid-19 severity or in hospital mortality among statins and non-user patients.[26]

Therefore, clinical trials and prospective studies are warranted in this regard to endorse the potential role of statins in Covid-19.

Conclusion

Statins therapy improves the outcomes of Covid-19 pneumonia through anti-inflammatory, immune-modulation, and in vitro anti-SARS-CoV-2 effects. As well, antiplatelet and antithrombotic effects may reduce Covid-19 induced-coagulopathy and progression of ARDS.

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