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Pros and cons for use of statins in people with coronavirus disease-19 (COVID-19)



Ray Subir ^a, Mukherjee Jagat J ^a, Gangopadhyay Kalyan K ^{b,*}

^a Department of Endocrinology and Diabetes, Apollo Gleneagles Hospitals, Kolkata, India

^b Department of Endocrinology and Diabetes, Fortis Hospital, Kolkata, India

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ABSTRACT

Background and aims: Morbidity and mortality from coronavirus disease 2019 (COVID-19) is higher among people with diabetes mellitus (DM), hypertension, and cardiovascular disease (CVD). Statins are used in the majority of people with DM and CVD. This mini-review discusses the current understanding of benefit-risk ratio of use of statins in COVID-19.

Methods: We searched PubMed database using specific keywords related to our aims till June 12, 2020. Full text of relevant articles published in English language were retrieved and reviewed.

Results: Statins, with their immunomodulatory, anti-inflammatory, anti-thrombotic, and anti-oxidant properties, have the potential to reduce severity of lung injury in, and mortality from, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) infections. Statin-induced upregulation of angiotensin-converting enzyme-2 (ACE2) has the potential to reduce lung injury from excess angiotensin II. By disrupting lipid rafts, statins have the potential to reduce viral entry into cells. However, benefit-risk ratio of its complex interaction with MYD88 gene expression on outcomes in COVID-19, and the putative role of low serum LDL cholesterol in increasing severity of SARS-CoV2 infection need further clarification.

Conclusions: People with COVID-19, who are already on statins for an underlying co-morbid condition, should continue on it unless there are specific contraindications. De-novo use of statins in people with COVID-19 with no underlying co-morbidity might be beneficial but awaits substantiation in clinical trials; till that time, de novo use of statins in COVID 19 should be limited to a clinical trial setting.

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1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2), can lead to multi-organ dysfunction and death in a few; elderly, and those with underlying co-morbidities, are particularly vulnerable. Li et al. reported a prevalence of diabetes mellitus (DM), cardiovascular disease (CVD) and hypertension of 9.7%, 16.4% and 17.1% among people hospitalized with COVID-19 [1]. The case fatality rate (CFR) in people with pre-existing DM and CVD was 7.3% and 10%–15% respectively, compared to an overall CFR of 2.3% among 72,314 people with COVID-19 [2]. Among other factors, it has been speculated that some of the medications used in these co-morbidities, namely dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1

receptor agonists, pioglitazone [3], angiotensin-converting enzyme inhibitors, angiotensin receptor blockers [4], and statins [5], might have an impact on outcome. Statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), are indicated, and widely used, in the majority of people with DM and CVD, primarily to reduce CVD events by treating hypercholesterolemia. However, statins also have immunomodulatory, anti-inflammatory, and anti-thrombotic effects, which has led some to propose their use to improve outcomes in COVID-19 [6]. However, others oppose this concept, suggesting harm [7]. In this article, we briefly review the current understanding of the benefit-risk ratio of use of statins in people with COVID-19.

2. Can use of statins be of benefit in people with COVID-19?

2.1. Statins and immunomodulation

Toll-like receptors (TLR) recognize pathogen-associated molecular patterns on viruses and other pathogens, and together with a

* Corresponding author. Diabetes & Endocrinology, Fortis Hospitals, 730, Eastern Metropolitan Bypass, Kolkata, 700107, India.

E-mail address: jaykal69@hotmail.com (G. Kalyan K).

set of adapter proteins, activate a signaling cascade that activates nuclear factor-kappa B (NF- κ B) to trigger innate immunity. Myeloid differentiation primary response 88 (MyD88) is the main adapter protein for the majority of TLRs [8].

Statins are known TLR-MyD88 pathway antagonists. They stabilize MyD88 levels during hypoxia and stress, thereby mitigating NF- κ B activation [9,10]. The effect of SARS-CoV2 on TLR-MyD88 pathway is largely unknown. However, extrapolating findings from studies with SARS-CoV, it is postulated that effect of statins on MYD88 gene expression might prevent SARS-CoV2 induced lung injury [5]. Interestingly, despite the many limitations of an observational study, Spigeleer et al. reported that statin intake among 153 elderly people with COVID-19 was significantly associated with absence of symptoms; the effect on long-stay hospitalization or death was positive but did not reach statistical significance (OR 0.75; CI 0.25–1.85) [11]. Overall, the small but significant benefit seen in this small observational study, and the theoretical potential for benefit from the immunomodulatory effects of statins, has already spurred a number of clinical trials to assess the effect of statins on outcomes in people with COVID-19 [12].

2.2. Statins, inflammation, and oxidative stress

Statins inhibit HMG-CoA reductase, which blocks the generation of mevalonate, the rate-limiting step in cholesterol synthesis. This results in the lowering of low-density lipoprotein (LDL) cholesterol, which in itself has an anti-inflammatory effect as LDL cholesterol is a strong promoter of inflammation [13]. Moreover, mevalonate is also a precursor of many isoprenoid compounds. Hence statins lead to a depletion of farnesyl pyrophosphate and geranylgeranyl pyrophosphate. This inhibition of prenylation of a variety of important cell-signalling small G-proteins leads to down-regulation of NF- κ B, suppression of cytokines and chemokines, with resultant anti-inflammatory effect [14]. Statins reduce the serum concentration of the systemic inflammatory bio-marker C-reactive protein (CRP). The evidence for benefit from these anti-inflammatory effects of statins was first realized in people with CVD. In the prospective pravastatin inflammation/CRP evaluation (PRINCE) RCT, pravastatin significantly reduced serum CRP levels at 12 and 24 weeks in subjects with or without CVD, largely independent of changes in LDL cholesterol levels [15]. Similarly, in the landmark JUPITER trial, rosuvastatin significantly reduced major cardiovascular events in healthy persons with LDLC <130 mg/dL and high-sensitivity C-reactive protein \geq 2 mg/dL [16]. The beneficial anti-inflammatory effects of statins, first noticed in the pathogenesis of atherosclerosis, led to their use in other inflammatory diseases, including rheumatoid arthritis, multiple sclerosis and uveitis [17].

Statins protect the vascular endothelium from oxidative damage. They increase the expression of endothelial nitric oxide synthase, and suppress pro-oxidant enzymes, such as NADPH oxidase, leading to reduction of reactive oxygen species [18]. By restoring redox balance in the vascular endothelium, statins reduce vascular inflammation triggered by oxidative stress.

Some researchers have postulated that the anti-inflammatory and anti-oxidant effects of statins might reduce lung injury in SARS-CoV2 infection. However, as yet, there are no animal or human studies to suggest that statins may reduce the severity of lung injury in people with COVID-19. Moreover, it is unclear whether the anti-inflammatory and anti-oxidant effects of statins are sufficiently strong enough to prevent SARS-CoV2 mediated lung injury. The atorvastatin as adjunctive therapy in COVID-19 (STATCO19) is an on-going RCT, looking at the effects of atorvastatin on disease progression and death at day-30 in people hospitalized with COVID-19, compared to standard care [12].

2.3. Statins and thrombosis

D-dimer levels are often elevated in people with COVID-19, and abnormal coagulation parameters are associated with poor prognosis; venous and arterial thrombotic events, including pulmonary embolism, deep vein thrombosis, ischemic stroke and myocardial infarction are common in people with COVID 19, reported among 31% of people with COVID-19 in one study [19]. Autopsy findings of non-survivors, who had elevated fibrinogen, prothrombin time, and D-dimer at presentation, revealed extensive involvement of peripheral pulmonary vasculature, multiple small thrombi, and oedema/haemorrhage in the lung parenchyma [20]. Statins have anti-platelet effects; they reduce platelet activation via both lipid-lowering and lipid-independent mechanisms [21]. Moreover, statins also have weak anti-thrombotic activity, which is mediated by a complex mechanism. Statins decrease tissue factor protein/activity, which converts factor X to factor Xa, and tissue plasminogen activator inhibitor-1, and increases the levels of tissue factor pathway inhibitor, thrombomodulin, activated protein C, and tissue plasminogen activator [22]. The theoretical benefit from this weak anti-thrombotic and anti-platelet activity of statins needs confirmation in clinical trials among people with COVID-19.

2.4. Statins and lipid rafts

SARS-CoV2 is an enveloped RNA virus. The S-protein in the viral membrane plays an important role in the initiation of infection by attaching to the angiotensin-converting enzyme 2 (ACE2) on the host cell membrane, followed by endocytosis of the virus. Membrane/lipid rafts (MLR) are cholesterol-rich areas of the plasma membrane that are important for membrane fusion and endocytosis. Glende et al., in an in-vitro study, showed that a substantial portion of ACE2 is associated with MLR, and a depletion of cholesterol from plasma membrane may disrupt these rafts resulting in reduced viral entry and infectivity [23]. Statin-induced reduction in the percentage of cholesterol in the plasma membrane might alter the assembly of ACE2 receptors, resulting in failure of internalization of the virus. Animal and cell line studies are urgently needed to assess the effect of statins on MLR and SARS-CoV2 cell-entry.

2.5. Statins and angiotensin-converting enzyme 2

Interestingly, on the one hand, as noted above, statins reduce viral entry in to the cell by altering the assembly of ACE2 by disrupting MLR, but on the other hand they have been shown in animal studies to upregulate the expression of ACE2 [24], with the potential for increasing viral entry into cells. However, the primary role of ACE2 is to degrade angiotensin II (Ang-II) to angiotensin 1-7 [Ang-(1-7)]. Ang-II promotes vasoconstriction, oxidative stress and inflammation, whereas Ang-(1-7) opposes these actions of Ang-II. SARS-CoV2 infection causes internalization of ACE2, resulting in a decrease in ACE2 at the cell surface, which leads to excess Ang-II action causing inflammation, tissue damage, fibrosis and loss of pulmonary function [4]. Like angiotensin receptor blockers [4], statins might reduce lung injury induced by excess Ang-II in people with COVID-19.

2.6. Statins and viral pneumonias

There is low to moderate quality evidence that statin use might decrease the severity of, and mortality from, viral pneumonias, possibly due to its immunomodulatory and anti-inflammatory effects [25]. Interestingly, a recent study, using computational molecular docking method, found that statins are efficient SARS-CoV2

main protease (Mpro) inhibitors [26]. SARS-CoV2 Mpro is a key protein in SARS-CoV2 life cycle; it cuts the polyproteins to yield functional viral proteins. However, more experiments and clinical studies are necessary to confirm this nascent concept of statins directly inhibiting the virus particle.

Keeping in mind the above beneficial effects of statins, several clinical trials have already been designed and registered at clinicaltrials.gov to study the effect of statins, either individually or in combination, on clinically relevant outcomes in people with SARS-CoV2 infection [27].

3. Can use of statins cause harm in people with COVID-19?

3.1. Serum total and LDL cholesterol levels and risk of SARS-CoV2 infection

Serum total, HDL, and LDL cholesterol levels were significantly lower among 71 people hospitalized for COVID-19 when compared to 80 matched healthy controls [28]. Commenting on this, Ravnskov has suggested that low serum LDL cholesterol predisposes to infections because LDL particles adhere to and inactivate microorganisms and their toxins [7]. The inverse association between serum cholesterol and morbidity and mortality from infectious diseases was separately noted in a meta-analysis of 19 cohort

studies including almost 70,000 deaths [29], and in a 15-year follow-up study of 120,000 adults [30]. Based on these associations, a few researchers have opined that by lowering LDL cholesterol levels, statins can increase morbidity and mortality in people with severe COVID-19 [7]. However, the quality of evidence for a causative role of low serum total and LDL cholesterol in increasing morbidity/mortality from infectious diseases, and in particular SARS-CoV2 infection, is low, and mostly derived from retrospective analyses of observational data, which are fraught with biases.

3.2. Effect of statins on innate immunity and its impact on SARS-CoV2 infection

In simplistic terms, the fact that statins are known TLR-MyD88 pathway antagonists, has led some to speculate that use of statins might interfere with innate immune response, and worsen SARS-CoV2 infection. However, as discussed above, the effect of statins on MYD88 gene expression, its role in innate and adaptive immunity, and the effect of such interactions on the severity of viral infection is complex. Moreover, the response might differ depending upon the infecting virus.

Table 1

Pros and cons for use of statins in people with COVID-19.

PROS		
Area of interest (REF)	Action of statins	Clinical effect in people with SARS-CoV2 infection
Immunomodulation [10]	Stabilization of MyD88 levels during hypoxia and stress, mitigating the action of NF-kB	Potential to reduce the severity of SARS-CoV2 infection
Inflammation [13,14]	1. Reduction of LDL cholesterol levels, thereby reducing direct LDL cholesterol mediated inflammation 2) Inhibition of prenylation of G proteins, leading to downregulation of NF-kB, suppression of pro-inflammatory cytokines (TNF α , IL-6) and chemokines (IL-8)	Potential role in reduction of SARS-CoV2 induced lung injury and protection from cytokine storm
Oxidative Stress [18]	Reduction of oxidative injury/maintenance of the redox balance of the endothelium by: 1) Upregulation of nitric oxide synthase 2) Suppression of pro-oxidant enzymes (NADPH oxidase)	Potential role in reduction of SARS-CoV2 induced lung injury
Thrombosis [21,22]	1. Anti-platelet effect (Lipid dependent and lipid independent mechanisms) 2. Weak anti-thrombotic effect 1) Prevents the conversion of factor X to Xa by downregulating tissue factor 2) Upregulation of thrombomodulin to bind thrombin	Potential to reduce/prevent venous and arterial thrombus formation
Membrane (lipid) rafts [23]	Disruption of lipid rafts by depletion of cholesterol from the plasma membrane, which might alter the assembly of angiotensin converting enzyme 2 receptors (act as co-receptors for SARS-CoV2 entry into the cell)	Theoretical possibility of reducing viral entry, leading to low viral titres and infectivity
Angiotensin converting enzyme 2 (ACE2) [4,24]	Upregulation of expression of ACE2	Potential to reduce SARS-CoV2 induced lung injury mediated by excess Angiotensin-II
SARS-CoV2 main protease [26]	Efficient inhibitors of SARS-CoV2 main protease (Computational molecular docking method)	Potential to directly inhibit the virus, reducing viral load
CONS		
Total and LDL cholesterol levels [7]	Reduction of serum total and LDL cholesterol	Speculated that this might increase morbidity/mortality from SARS-CoV2 infection, as elevated LDL cholesterol is protective since LDL particles adhere to and inactivate microorganisms and their toxins
Immunomodulation [10]	Inhibition of MyD88 expression	Speculated to reduce innate immunity response, thereby worsening SARS-CoV2 infection
Angiotensin converting enzyme 2 (ACE2) [24]	Upregulation of expression of ACE2	Potential to increase SARS-CoV2 entry into cells
Myositis and liver dysfunction [31–34]	1. Mild elevation of liver enzymes in 10%, and elevation >3 times upper limit of normal in 1%–3% 2. Myalgia in 2%–7%	Detrimental effect in people with COVID-19 with skeletal muscle symptoms or liver dysfunction
Drug interactions [35,37]	Inhibition of cytochrome P-450 group of enzymes by protease inhibitors used in COVID-19 may significantly increase statin levels	Increased risk of toxicity: myopathy and rhabdomyolysis

3.3. Interaction between statin-induced adverse events and manifestations in COVID-19

Muscle symptoms/toxicity, and liver dysfunction, are the two prominent, albeit rare, adverse effects of statin therapy. Muscle symptoms generally occur within one month of initiation of therapy, with myalgia being reported in 2%–7% of people on statins [31]. People with severe COVID-19 might have skeletal muscle involvement with elevated serum creatine phosphokinase, reported in 19.3% of such patients in one series [32], or frank rhabdomyolysis; it is essential to discontinue statins in people with COVID-19 with skeletal muscle symptoms. Although serious hepatotoxicity is rare, statins cause mild elevation in liver enzymes in 10%, and elevation more than three times the upper limit of normal in 1%–3% of people [33]. Elevated liver enzymes have been recorded in 16%–53% of people with moderate to severe COVID-19 [34]. It is essential to discontinue statin therapy in people with COVID-19 with elevated liver enzymes.

3.4. Drug interactions

Use of protease inhibitors like lopinavir/ritonavir in COVID-19, which are potent inhibitors of cytochrome P-450 system of enzymes, inhibit the metabolism of most statins, thereby significantly increasing their serum levels, with the potential for increased toxicity [35]. Maximum daily dose of 20 mg for atorvastatin, and 10 mg for rosuvastatin, have been proposed when used together with such protease inhibitors [36]. Rare instances of rhabdomyolysis have been reported due to statin-azithromycin interaction [37].

4. Conclusions (Table 1)

Most people with T2DM, CVD, and hypertension are on statins. We suggest that people with COVID-19, who are already on a statin for an underlying co-morbid condition, should continue on it because cardiovascular complications, including myocarditis, myocardial infarction and venous thromboembolic events are common in people with COVID-19. Statins should be discontinued if there is myositis and/or liver dysfunction, and their dose must be appropriately reduced when drugs that inhibit cytochrome P-450 system are in use.

De-novo use of statins in people with COVID-19 might be beneficial but needs substantiation. Theoretically, the pleiotropic properties of statins, including its immunomodulatory, anti-inflammatory, anti-thrombotic, and anti-oxidant effects might reduce the severity of SARS-CoV2 infection. Moreover, by inhibiting SARS-CoV2 main protease, statins might have a direct effect on the virus particle. Statins might also have a potential role in reducing viral entry into the cells by interfering with the cholesterol bridges on the cell wall. However, the benefit-risk ratio of its complex interaction with MYD88 gene expression on outcome in COVID-19, and the role of low serum LDL cholesterol on putative increase in severity of COVID-19 needs further clarification. In balance, although the benefit-risk ratio for use of statins in COVID-19 is in its favor, the unresolved issues, albeit minor, do not allow us to recommend routine *de-novo* use of statins in all people with COVID-19. Till further evidence from on-going trials is available, it is prudent to use *de-novo* statins in COVID-19 only in a clinical trial setting.

COVID-19: coronavirus disease-19; SARS-CoV2: severe acute respiratory syndrome coronavirus 2; MyD 88: myeloid differentiation primary response 88; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; TNF- α : tumor necrosis factor- α ; IL -6, 8 interleukin 6,8; NADPH: nicotinamide adenine dinucleotide phosphate reduced form; ACE: angiotensin converting

enzyme; LDL: Low-density lipoprotein cholesterol.

Declaration of competing interest

No conflict of interest to declare.

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