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Statins: unexpected help in COVID-19

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Abstract

The COVID-19 pandemic has had a huge impact on the health of millions of people around the world on an unprecedented scale. Unfortunately, the process of creating effective antiviral drugs and vaccines is being delayed. Therefore, drugs that are already available and may have an effect on COVID-19 are being investigated. Due to the fact that viral infection often affects the cardiovascular system, causing myocardial infarction, viral myocarditis, tachyarrhythmias and stress cardiomyopathies, a theory was put forward that HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA reductase) inhibitors (statins) can reduce the risk of cardiovascular complications in these patients. In recent years, this class of drugs has been proposed, including for viral infections, such as the influenza virus or MERS-CoV. The review discusses both the latest clinical data on the efficacy of statins in COVID-19 and the pleotropic mechanisms of statins that can limit the pathogenic effect of viruses. In particular, statins can act on lipid cell rafts (subdomains of the plasma membrane), decreasing their lipid concentration; limiting the interaction of the virus with the receptors of angiotensin-converting enzyme-2 and CD-147. Statins have an anti-inflammatory effect (blocking the molecular mechanisms of inflammation, including NF-κB and NLRP3), limit the development of a "cytokine storm" in severe patients with COVID-19; can inhibit SARS-CoV-2 basic protease; influence coagulation, limit sympathetic activity and have other effects. In two large cohort observational studies (n = 96032 and n = 13981), hospitalized patients with COVID-19 who were taking statins showed a decrease in hospital mortality and mortality 28 days after the admission to the hospital. Thus, statins can play a role in the treatment of COVID-19.

Key words: statins, pleotropic effects, COVID-19, angiotensin-converting enzyme 2, CD 147, mortality, lipid rafts, inflammation

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Статины: неожиданная помощь при COVID-19

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Резюме

Пандемия COVID-19 оказала беспрецедентное воздействие на здоровье миллионов людей во всем мире. К сожалению, затягивается процесс создания эффективных противовирусных препаратов и вакцины. Поэтому исследуются уже имеющиеся в наличии лекарственные препараты, которые могут оказать эффект при COVID-19. В связи с тем, что вирусная инфекция часто поражает сердечно-сосудистую систему, вызывая инфаркты миокарда, вирусные миокардиты, тахиаритмии и стрессовые кардиомиопатии, была выдвинута теория, что ингибиторы 3-гидрокси-3-метилглютарил-кофермент А редуктазы (ГМГ-КоА-редуктазы) — статины — способны снизить риск развития сердечно-сосудистых осложнений. В последние годы данный класс препаратов был предложен в том числе при вирусных инфекциях, таких как вирус гриппа или MERS-CoV. В обзоре обсуждаются как последние клинические данные об эффективности статинов при COVID-19, так и их плейотропные механизмы, способные ограничить патогенное действие вирусов на организм. В частности, статины могут действовать на липидные клеточные рафты (субдоменов плазматической мембраны), снижая в них концентрацию липидов; ограничивать взаимодействие вируса с рецепторами ангиотензинпревращающего фермента-2 и CD-147; обладают противовоспалительным эффектом (блокировка молекулярных механизмов воспаления, включая NF-κB и NLRP3); ограничивают развитие «цитокинового шторма» у тяжелых пациентов с COVID-19; могут ингибировать основную протеазу SARS-CoV-2, влиять на коагуляцию, ограничивать симпатическую активность нервной системы и так далее. В двух крупных когортных наблюдательных исследованиях (96032 и 13981 больных) у госпитализированных пациентов с COVID-19, принимающих статины, было показано снижение внутрибольничной смертности и смертности через 28 дней после начала госпитализации. Таким образом, данная группа препаратов может занять свое место в лечении COVID-19.

Ключевые слова: статины, плейотропные эффекты, COVID-19, ангиотензинпревращающий фермент 2, CD 149, смертность, липидные рафты, воспаление

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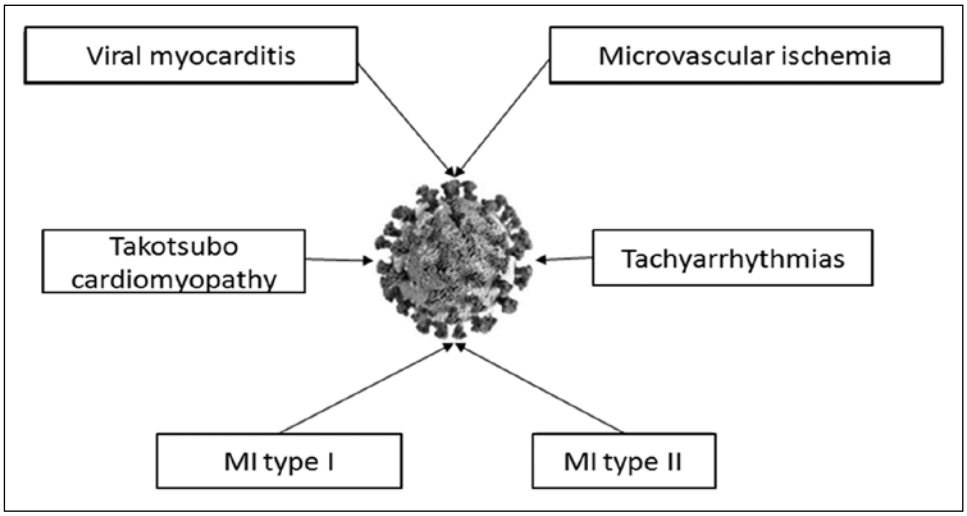
The new coronavirus, which induces acute severe respiratory syndrome (SARS-CoV-2) and triggered the COVID-19 pandemic, poses a huge challenge to the healthcare system around the world. Currently, there is no effective pathogenetic treatment for COVID-19, and the most effective preventive strategy is to prevent exposure to the virus [1, 2]. Cardiovascular diseases (CVD) prevention and treatment strategies are extremely important in the COVID-19 pandemic. It is already clear that the development of pathogenetic therapy and vaccines against the virus will take a long time. Maximizing the use of already available drugs that can have antiCOVID-19 activity is one of the most effective treatment strategies More than 850 clinical trials have now been launched on already available medicines for the treatment of COVID-19. Statins, HMG-CoA reductase inhibitors, are a group of drugs commonly used to lower serum cholesterol levels by preventing its synthesis in the liver [3, 4]. In addition to the well-known anti-lipidemic effects, statins have beneficial pleiotropic effects. They regulate numerous biological pathways involved in antioxidant, anti-inflammatory, and antitumor cellular responses [3]. Statins have been shown to reduce mortality effectively and improve the course of a new coronavirus infection (CVI) according to recently emerging data in prospective clinical trials.

This review presents data on the positive effect of statins in COVID-19 and reveals some of their pathophysiological protective mechanisms.

COVID-19 and cardiovascular damage

Patients with CVD are at high risk of severe viral infection and mortality [5]. On the other hand, there is sufficient evidence that viral infections, in particular COVID-19, can damage the cardiovascular system [6, 7–9] (Fig. 1). Several independent studies showed signs of myocardial damage in COVID-19 in 7.2–29.0 % of patients [8, 9]. In particular, Guo et al. identified myocardial injury in 27.8 % of patients with COVID-19 [6]. According to Shi and co-authors, the acute inflammatory response is typical for COVID-19, increases the inflammatory activity within atherosclerotic plaques, causes endothelial dysfunction, which leads to atherothrombotic complications, exacerbates existing myocardial ischemia, and causes myocardial damage [8]. In the upper part of Figure 2, some well described pathogenetic mechanisms are presented that affect the damage to the cardiovascular system in COVID-19: hypotension, systemic inflammatory response, development of disseminated intravascular coagulation, hypoxia, ischemia, endothelial dysfunction, dysfunction of the renin-angiotensin system, cytokine storm and hypersympathicotonia [10]. Therefore, cardiovascular complications of viral infection may include type 1 and type 2 myocardial infarction, viral myocarditis, induction of tachyarrhythmias, and stress cardiomyopathy. [6, 7–9, 11].

Figure 1. The damage to the cardiovascular system in COVID-19



Note: MI — myocardial infarction.

Effects of statins beyond lipid reduction

Statins are first-line lipid-lowering medications with relatively few side effects, low cost, and widely available worldwide. The powerful anti-inflammatory and immunomodulatory effects of HMG-COA reductase inhibitors suggest that they may be useful for countering coronavirus infections, including SARS-CoV-2 [12]. In addition to the antilipidemic and antiatherosclerosis effects, the pleiotropic effects of statins include a reduction of chronic non-immune inflammation, including those in the arterial wall. [13, 14]. These effects may be useful for preventing the cytokine storm caused by COVID-19 [5]. The anti-inflammatory non-lipid effects of statins have been confirmed in large randomized clinical trials, such as AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) or JUPITER (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin), in which statins reduced C-reactive protein levels independently of low-density lipoproteins (LDL) [15]. Also, the JUPITER study showed that treatment with rosuvastatin could reduce the incidence of pneumonia in healthy adults with low LDL (< 130 mg/DL) and high C-reactive protein ≥ 2.0 mg/DL [16]. Thus, there is a scientific background for investigating the effectiveness of statins in COVID-19.

COVID-19, respiratory diseases, and statins

Since the discovery of statins, they have been proposed as therapeutic agents for various diseases, including viral infections such as seasonal influenza virus or MERS-CoV [17, 18]. A study of 1,055 adult patients with viral pneumonia revealed lower mortality rates and intubation rates when using statins throughout their hospital stay (odds ratio (or) 0.26; 95% confidence interval (CI) 0.08–0.81) [19]. A meta-analysis by Chopra and co-authors found that statin use was associated with lower mortality after pneumonia (OR 0.62, 95% CI: 0.54–0.71) [20]. Makris and co-authors investigated the effect of pravastatin therapy on the incidence and mortality in patients with artificial ventilation [21]. In the pravastatin group, the probability of survival significantly increased compared to the control group during the 30-day treatment period (p = 0.04), and the incidence of fan-associated pneumonia decreased (25.3% vs. 38.2%). The positive role of statins in the prevention of sepsis in community-acquired infections has been confirmed in other studies [22].

COVID-19, lipid rafts, and statins

The SARS-CoV-2 coronavirus is a single-stranded RNA virus covered with a lipid envelope. The virus has four structural proteins: nucleocapsid protein, membrane protein, envelope protein, and spike protein (S-glycoprotein), which provides attachment to the angiotensin-converting enzyme-2 (ACE 2) and CD 147 receptor [23]. In order to understand the possible role of statins in the treatment of COVID-19, it is necessary to investigate possible interaction of the virus with the cell membrane.

Lipid rafts are subdomains of the plasma membrane of cells that are rich in cholesterol and glycosphingolipids. The important role of membrane lipids in the attachment of viruses, including some coronaviruses, to host cells has been reported [24, 25], as well as the fact that an increase in the concentration of cholesterol in lipid rafts increases viral infectivity [26]. Lipid rafts play a role in the interaction of the s-protein ("spike") and the ACE 2 receptor, and for the processes of viral endocytosis [27]. The role of cholesterol in viral penetration has been studied for several coronaviruses, including SARS-CoV [27]. Cholesterol, which is present in the cell membrane and viral envelope, contributes to replicating of the coronavirus, acting as a key component in the penetration of the virus [6, 23].Simultaneously, it was noted that the cholesterol level in patients with COVID-19 was extremely variable. In particular, during the acute phase of COVID-19, total cholesterol and LDL levels decreased sharply compared to the baseline level [28]. On the other hand, a dramatic decrease of cholesterol level in SARS-CoV infection was followed by significant decrease of viral microRNA concentration [29] and dysfunction of virus's fusion with the cell membrane [27].

Statins inhibit cholesterol biosynthesis by inhibiting HMG-CoA reductase and modulate the lipid composition of the cell membrane. Atorvastatin reversed many of the lipid raft-associated changes caused by systemic lupus erythematosus [30]. Therefore, it is possible to use statins to prevent changes in the lipid membrane in host cells caused by COVID-19 infection, reducing the rate of viral replication.

COVID-19, ACE 2, and CD 147 virus receptors and statins

Although ACE 2 is especially prevalent in the heart and kidneys [31], where it plays an important role in blood pressure control [32], it is also present in other tissues, including the lungs [31]. For this reason, dysregulation of ACE 2 levels can lead to undesirable and even fatal results. For example, disruption of ACE 2 expression increased vascular permeability and pulmonary edema, contributing to the lung damage [33]. Therefore, the antiCOVID-19 therapeutic strategies are proposed basing on virus interaction with ACE 2 and other receptors [34]. Statins are known to increase the level of ACE 2 in tissues — in a model of experimental atherosclerosis, and atorvastatin increased the levels of ACE 2 protein in the heart and kidney tissue [35]. The cell receptor CD 147 can also bind to the S-glycoprotein, the "spike" of the SARS-CoV-2 coronavirus [36] and the pleiotropic effect of statins could associated with a modulation of expression, structure and function of CD 147. Atorvastatin reduced CD 147 levels and increased the stability of atherosclerotic plaques in a model of experimental atherosclerosis [37]. Thereby, there are evidences that statins can affect the SARS-CoV-2 ability to infect by modulating receptors CD 147 and ACE 2 in human cells.

COVID-19, inflammation, and statins

One of the most typical pleiotropic effects of statins is their anti-inflammatory effect [3]. It is believed that limiting vascular inflammation, in addition to their lipid-lowering effects, contributes to the beneficial effects of statins on cardiovascular outcomes [38]. Atorvastatin inhibits the activation of NF-κB-mediated induction of cytokines induced by angiotensin II or tumor necrosis factor-α [39]. Several studies have shown the ability of HMG-CoA reductase inhibitors to regulate NLRP3 inflammation [40]. Also, in patients with CVD, statin treatment suppressed the expression of the cytokines NLRP3 and IL-18 and IL-1β [41]. Therefore, the anti-inflammatory effect of statins, in particular concerning NF-κB and the NLRP3 inflammatory pathways, will be an important component of the pleiotropic effect of these drugs in COVID-19.

COVID-19, coagulation, and statins

The coagulation system can limit the spread of pathogenic microorganisms during severe infections, as exemplified by many viruses such as HIV, Dengue virus, or Ebola [42]. However, coagulation disorders are common in acute viremia. In patients infected with SARS-CoV-1, vascular endothelial damage, disseminated intravascular coagulation, deep venous thrombosis, and pulmonary embolism were observed, leading to pulmonary infarction [43]. In particular, the patients showed an increase in the activated partial thromboplastin and prothrombin time and D-dimer [44]. Based on these data, the prophylactic and therapeutic use of antithrombotic drugs was initiated, and now Low-molecular-weight heparins are included in all protocols for the treatment of severe patients with COVID-19. One of the numerous statins` pleiotropic effects is the modulation of the activation of coagulation cascade. Fluvastatin and rosuvastatin block tissue factor activity and, therefore, affect the coagulation process [45]. Thus, one of the potential mechanisms of statin's efficacy in COVID-19 may be antithrombotic effects.

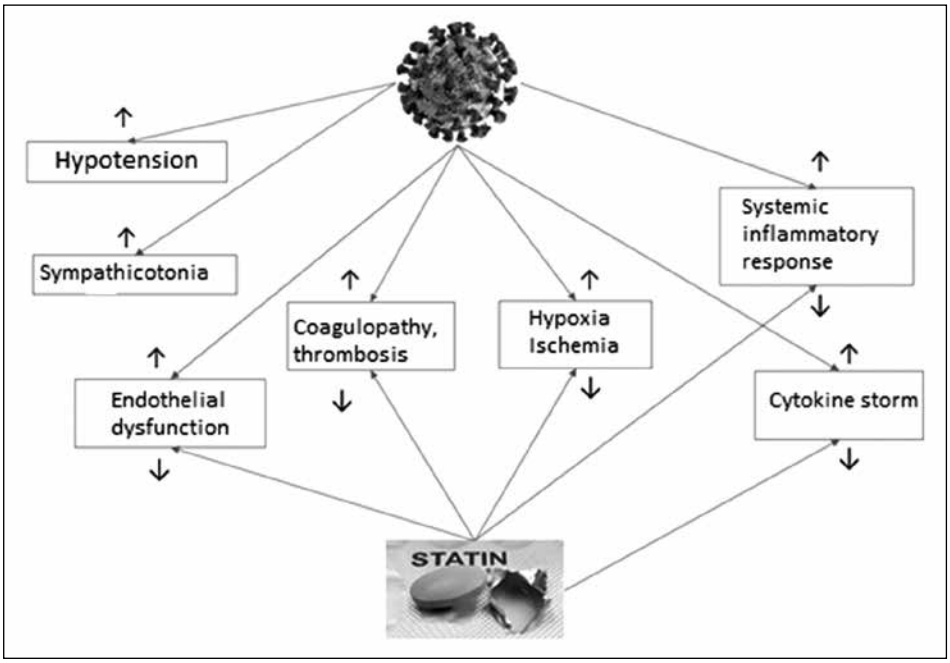
Effects of statins on COVID-19 mortality

A recent cohort study of 96,032 hospitalized patients with COVID-19 showed a positive effect of statins on hospital mortality. There were more survivors in the HMG-CoA reductase inhibitor group than in the control group (10.0 % versus 6.9 %, $p < 0.0001$). Thus, the statins were shown to be an independent predictor of in-hospital mortality (HR, 95 % CI: 0.793, 0.736–0.855) [46]. A in large retrospective cohort study of 13981 COVID-19 hospitalized patients the association of statin use with clinical outcomes was shown [47]. Since the study was uncontrolled, the groups also differed in age and the presence of comorbidities. The most commonly used statins were atorvastatin (83.2 % of all statins) and rosuvastatin (15.6 %). As a result, mortality by the 28th day of observation from the moment of hospitalization was lower in the statin against non-statin group (5.5 % versus 6.8 %, respectively, $p = 0.046$).

Discussion

Statins can be used in clinical practice as a pathogenetic or additional method of treatment for both dyslipidemia and coronary heart disease, as well as diabetes mellitus, strokes, arterial hypertension, chronic kidney disease, various types of cancer, rheumatoid arthritis, asthma, chronic ob-

Figure 2. Statins and COVID-19 pathophysiological processes



structive disease lungs and even some infectious diseases (malaria, Ebola, diseases associated with the influenza virus, or MERS) [48] as part of the main indications for this class of drugs. Therefore, based on large number of pleiotropic effects and the widespread use of HMG-CoA reductase inhibitors throughout the world, an assumption has emerged about the possible positive effect of therapy with these drugs in patients with COVID-19. In this review we discussed some of the statins' pleiotropic effects, such as modulation of ACE 2 and CD 147 receptors, lipid cell rafts, decrease of the inflammatory response, and hypercoagulability (Fig. 2). In addition to the issues discussed, a decrease in sympathetic tone by this class of drugs can be noted [49] and the fact that some inhibitors of HMG-CoA reductase can serve as potential inhibitors of the main protease SARS-CoV-2 [50]. In two cohort studies, statins in patients with COVID-19 have been shown to reduce mortality [46, 47]. However, at the moment, statin use for COVID-19 still falls under the off-label category. Several randomized clinical trials are currently underway with COVID-19 patients using simvastatin in combination with the JAK-1/2 inhibitor ruxolitinib (NCT04348695) and atorvastatin (NCT04380402) to support this theory. However, the muscle symptoms often found in COVID-19 can mimic muscular side effects of the drugs. Thus, basing on the mechanisms of statin action, the drugs may be effective in high-risk patients with severe COVID-19, which requires confirmation in randomized control trials.

Conflict of interest

The authors declare no conflict of interest.

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