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Pleyotropic Effects of Statins Non-Alcoholic Fat Disease of the Liver Non-Alcoholic Steatohepatitis

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Abstract

Hypolipidemic preparations and non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and lipid-related pathologies have a complex relationship that results in liver damage. In recent years, studies have been carried out to determine the effectiveness of statins in NAFLD/NASH in the treatment and prevention of their adverse effects. Scientific observations were made to assess the effects of statins on NAFLD/NASH, followed by an analysis of their pleyotropic effects on liver function. Several studies have shown decreases in NAFLD/NASH-associated inflammation and fibrosis in the treatment of statins. These anti-inflammatory and anti-fibrous effects were due to their pleyotropic properties, which were observed in addition to the hypolipidemic effect. In various animal studies, statins have been found to reduce liver lipotoxicity, oxidative stress, inflammatory reactions, and associated with fibrosis with NHA in several ways. Statins provide these protective effects by restoring the expression of the alpha receptor gene activated by peroxysomal proliferator (PPAR α) and thus reducing mitochondrial and peroxysomal oxidation of fatty acids (FAO). Statins also increased paraoxonase 1 (PON1), antioxidant, and antiatherogenic enzyme, which decreases with NAVBP, as well as liver lipotoxicity by separating cholesterol crystals and Kupfer cells (KC) from coronogenic structures (CLS). They exhibit anti-tumor properties by inhibiting inflammatory cytokines and vascular proliferative factors. Moreover, they have restored healthy sinusoidal liver endothelial cells (LSEC) and stellated liver cells (HSC), along with inhibiting HSC activation by modulating the induced synthase of nitrogen oxide (iNOS) and expressing the endothelial synthase of nitrogen oxide (eNOS). In addition, they protected against cardiovascular disease (GCC) and mortality, hepatocellular carcinoma (GCC) and metabolic syndrome (MS) associated with NHA/NHA. NHA and its predecessor, NHA, can be treated and prevented with statins, due to its pleyotropic properties. This study helps to prove and successfully explain the substance. Once confirmed by major human clinical trials, this could revolutionize NASG therapy.

Keywords: NAFLD/NASH, steatosis, fatty acid oxidation, cytokines, SARS-CoV-2, statins

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Плейотропные эффекты статинов при неалкогольной болезни печени и неалкогольном стеатогепатите

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Резюме

Гиполипидемические препараты и неалкогольная жировая болезнь печени (НАЖБП), неалкогольный стеатогепатит (НАСГ), патологии, связанные с липидами, имеют сложную взаимосвязь, которая приводит к повреждению печени. В последние годы появляются исследования, которые направлены на определение эффективности статинов при НАЖБП/НАСГ в лечении и профилактике связанных с ними неблагоприятных исходов. Были проведены научные наблюдения, оценивающие влияние статинов на НАЖБП/НАСГ, а затем проведен анализ их плейотропного влияния на функции печени. Несколько исследований продемонстрировали снижение НАЖБП/НАСГ-ассоциированного воспаления и фиброза при лечении статинами. Эти противовоспалительные и противифиброзные эффекты были получены за счет их плейотропных свойств, которые наблюдались в дополнение к гиполипидемическому эффекту. В различных исследованиях на животных было обнаружено, что статины уменьшают липотоксичность печени, окислительный стресс, воспалительные реакции и связанный с фиброзом НАСГ. Статины оказывают эти защитные эффекты, восстанавливая уровень экспрессии гена рецептора альфа, активируемого пероксисомальным пролифератором (PPAR α), и таким образом восстанавливают митохондриальное и пероксисомальное окисление жирных кислот (ФАО). Статины также увеличивали уровень параоксоназы-1 (PON1), антиоксиданта и антиатерогенный фермент, уровень которого снижается при НАЖБП, а также проявляется липотоксичность печени путем разделения кристаллов холестерина и клеток Купфера (KC) с короноподобными структурами (CLS). Они проявляют противоопухолевые свойства, ингибируя провоспалительные цитокины и сосудистые пролиферативные факторы. Более того, они восстановили здоровые синусоидальные эндотелиальные клетки печени (LSEC) и звездчатые клетки печени (HSC) наряду с ингибированием активации HSC посредством модуляции индуцированной синтазы оксида азота (iNOS) и экспрессии эндотелиальной синтазы оксида азота (eNOS). Кроме того, они защищали от сердечно-сосудистых заболеваний (ССЗ) и смертности, гепатоцеллюлярной карциномы (ГЦК) и метаболического синдрома (МС), связанных с НАЖБП/НАСГ. НАСГ и его предшественник НАЖБП можно лечить и предотвращать с помощью статинов, благодаря плейотропным свойствам. Если бы все вышесказанное однажды было подтверждено крупными клиническими испытаниями на людях, это могло бы произвести революцию в терапии НАСГ.

Ключевые слова: НАЖБП/НАСГ, стеатоз, окисление жирных кислот, цитокины, SARS-CoV-2, статины

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of liver disease worldwide becoming the most frequent indication for liver transplantation due to progression of non-alcoholic steatohepatitis (NASH). It affects 25% of adults worldwide [1]. NAFLD is characterised by fat accumulation (>5%) in hepatocytes called liver steatosis, without other causes of liver disease such as viral hepatitis, increased alcohol consumption or any chronic liver disease [2]. But it can progress to NASH or steatohepatitis, which is a liver steatosis with severe liver damage (canine degeneration of hepatocytes), inflammation of the liver and fibrosis. Further progression can lead to liver lesions, liver cirrhosis, terminal liver disease, portal hypertension (PG) and, in rare cases, hepatocellular carcinoma (HCC). NAFLD/NASH is also associated with other diseases. Such as metabolic syndrome (MS), cardiovascular disease (CD), diabetes mellitus (DM) and obesity [3]. Being closely related to insulin resistance (IR) and central obesity, NAFLD is considered to be an increased risk of cardiovascular disease, especially atherosclerosis. In fact, NAFLD/NASH has the highest risk of death in NAFLD/NASH patients with cardiovascular disease than just liver disease. The development of NAFLD and its progression to NASH is not well understood. Various factors affecting the development of liver steatosis and its progression to NASH may be related to the availability of free fatty acid (FFA) due to IR and increased peripheral lipolysis, increased synthesis and reduced exports of triglycerides via very low density lipoproteins (VLDLP), inflammatory cytokines and adipokines, oxidative stress of the liver, mitochondrial and peroxisomal dysfunction, and from intestinal microbiota [4]. Intrahepatic fibrosis is an established risk factor for cirrhosis, hepatocellular carcinoma and life-threatening liver failure. At present, the main treatment for NAFLD/NASH is a change in lifestyle with reduced caloric intake, weight loss and exercise. No pharmacological treatment has been approved, there are still no standards for the treatment of FGM, but the use of insulin-stabilizing drugs, hypolipidemics and antioxidants is practiced [9]. Pharmacotherapy, aimed at the underlying pathophysiology of this increasingly common disease, must be found and can stop its progression with lethal outcomes. Statins may be a strong candidate from this point of view, since they are lipid-reducing and general cholesterol-reducing agents that are 3-hydroxymethylglutaryl-coenzyme A (HMG CoA) reduction inhibitors, an enzyme that limits the rate of cholesterol synthesis. They are also pleiotropic. Their pleiotropic effects include anti-inflammatory, anti-proliferative, antioxidant, etc. as well as antithrombotic, anti-cancer and immunomodulating, which reduces inflammation and fibrosis in patients with NAFLD/NASH [10]. According to various studies, statins reduce hepatic steatosis by reducing oxidative stress and by increasing hepatic antioxidant paraoxanase1 (PON1) [11] and increasing mitochondrial and peroxisomal oxidation and induction of alpha receptor, Genome-activated peroxide proliferation (PPAR α), fatty acid oxidation (FAO) [12]. They also reduce hepatic inflammation by reducing the expression of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF- α), interleukin 6 (IL-6), and transforming growth factor beta 1 (TGF- β 1) [13]. In addition, statins reduce fibrogenesis in HCC by improving endothelial dysfunction with the recovery of sinusoidal liver space and stabilization of stellate cells, as well as increasing nitrogen endothelial oxide content and synthase activity (eNOS) [14–16]. Statins are thought to protect against GTC as they reduce the expression in the liver of angiogenic factors such as the receptor of the vascular endothelial growth factor (VEGFR), the epidermal growth factor receptor (EGFR) and the platelet growth factor (PDGF) [13]. In addition, statins also reduce the level of [17] isoprenoids and eliminate cholesterol crystals, corona-like structures (CLS) [18]

and inactivate stellated liver cells (HSC) [19] that prevent inflammation and fibrosis in NAVP/HAZG. In addition to the above, statins can play an important role in preventing, delaying and converting liver steatose into NHA.

In addition, it has been reported that treatment with statins reduces the risk of atherosclerosis and mortality from CCS associated with NAFLD. In other words, they are the only class of anti-hyperlipidemic agents that reduce CCS at NAFLD [21]. Statins are generally considered to be antihyperlipidemic and their pleyotropic properties are not well understood. The study aims to review the medical literature to identify various pathogenic micro-organisms, the pathways of NAFLD progression to NASH, and the effectiveness of the statins in such cases. We hope this will help to justify a more diversified use of statins and subsequently raise awareness of their use in NAFLD and NASH. As NAFLD/NASH becomes a growing public health problem. To prevent and effectively treat statins, use can be a breakthrough because NASH has the highest risk of cardiovascular disease. But dyslipidemia also remains insufficiently studied for treatment. In the last year, there have also been a number of scientific articles on the use of statins in the complex treatment of SARS-CoV-2 and the outcome of pneumonia caused by this virus.

Pathogenesis COVID-19

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2), which is present on type II pneumocytes in the lungs and on cell surfaces in the endothelial of the heart and vessels. The viral infection is facilitated by the interaction of the receptor-binding domain in its ectodomain of viral spike glycoprotein with ACE2 receptors [22, 23]. Within cells, the virus is replicated, followed by exocytosis and release of mature viruses [22]. The endocytic activity involved in the penetration of the injectable virus activates the activity of the domains 17 disintegrin and metalloprotease (ADAM17), which removes ACE2 from the cell membrane. ACE2 is responsible for the transformation of angiotensin II into angiotensin 1–7, which has several benefits including vascular, anti-inflammatory and antifibrotic [9, 24]. Consequently, the reduced availability of ACE2 on the cell surface results in the loss of ACE2-mediated protection from the harmful effects of tissue renin angiotensin-aldosterone.

SARS-CoV-2 can also cause multi-system inflammatory disease, a cascade due to a cytokine storm by activating IL-6, IL-8, TNF- α . A cascade of an inflammatory process is launched, leading to an increase in the production of pro-inflammatory agents such as interleukin-1 (IL-1), IL-2, IL-3, IL-4, IL-6, which cause increased vessel permeability, alveolar damage to epithelium, etc. leading to acute respiratory distress syndrome [16, 22]. COVID-19 infections also lead to coagulopathy and thromboembolism complications such as systemic venous thrombosis and pulmonary embolism.

Possible Static Mechanisms at COVID-19. Statins have several different effects related to COVID-19.

Anti-inflammatory effect. As anti-inflammatory agents, statins inhibit isoprenoid synthesis, which plays an important role in inflammation. Statins inhibit leukocyte adhesion, activation of T cell molecule [25]. Statins reduce the expression of proinflammatory cytokines such as IL-6, IL-8 and chemotaxis protein-1 monocytes, thereby altering the inflammatory path of damage to host cells [11, 12, 26].

Antithrombotic and vascular wall effects. Statins are known to increase nitric oxide production, improve vascular endothelial function and have antithrombotic

effects by inhibiting platelet aggregation and minimizing the production of mediators of provocants [27].

Impact on virus cell penetration. Several different theories have been proposed to describe the potential effects of statins on the penetration of SARS-CoV-2 into human cells. Both beneficial and adverse effects were proposed.

The role of cholesterol in cell membranes. The SARS-CoV-2 binding spikes to ACE2 receptors present on cell surfaces are facilitated by the presence of lipid rafts on cell membranes. Cholesterol depletion of cell membranes with agents such as cyclodextrin has been shown to inhibit the process and prevent the virus from entering cells. Conversely, the enrichment of cell membranes with cholesterol may contribute to the spread of the virus [28, 29].

The effect of statins on cholesterol in cell membranes is already known. Some researchers believe that statins, by reducing endogenous cholesterol synthesis, deplete cell membranes and reduce cholesterol [30]. In contrast, other researchers have suggested that decreasing circulating cholesterol increases regulation of low-density lipoprotein receptors on the cell surface, thereby increasing cholesterol uptake from blood [14, 17]. Statins also inhibit acyl CoA: cholesterol acyltransferase (ACAT) present in the endoplasmic reticulum, which is also responsible for the removal of cholesterol from cell membranes. A recent study has shown that SARS-CoV-2 causes one of the interferon-stimulated genes of cholesterol-25-hydroxylase (CH25H) in vitro and in patients with COVID-19. CH25H turns cholesterol into 25-hydrocholesterol (25HC), which activates ACAT, thus preventing the fusion of SARS-CoV-2 to cell membranes and the virus from entering cells. The effect of 25HC on preventing uptake in lung epithelial cells has been specifically demonstrated [27]. However, studies using human culture respiratory epithelium cells have shown that statins such as fluvastatin successfully inhibit the penetration of SARS-CoV-2 into cells [20].

Influence on expression iAPP

Statins, like APP inhibitors and angiotensin receptor blockers, are known to increase ACE2 regulation by expressing on human cells [5, 6]. It has been suggested that this effect may increase susceptibility to SARS-CoV-2 infection. Conversely, increased expression of ACE2 is expected to be a beneficial effect rather than a harmful one [10, 23]. ACE2-mediated transformation of angiotensin II to angiotensin I [12, 19] takes place as shown, thus minimizing lung damage in patients infected with coronavirus [31].

Other mechanisms. Recent studies have suggested that statins inhibit the main protease of SARS-CoV-2 (Mpro), i.e. the key enzyme of the coronavirus [26]. Disruption of this protease activity can affect viral infection by inhibiting viral glycoprotein. However, it is not clear whether this effect is also observed at statin concentrations in doses used in clinical conditions.

Cardiovascular advantages

Epidemiological studies have shown that patients with pre-existing cardiovascular disease are at greater risk of infection as well as of developing severe COVID-19 [27, 28]. At the same time, COVID-19 itself can lead to a number of cardiovascular complications. Statins have a well-known effectiveness in reducing the risk of cardiovascular events in a wide range of patients [19, 25]. Therefore, in addition to any potential direct effects of

statins on COVID-19, statins as such help reduce the risk of cardiovascular complications in these patients and improve the clinical course of the disease and outcome.

Clinical results of statins at COVID-19

Several observational studies have evaluated the potentially positive role of statins in COVID-19 [32]. Zhang et al. conducted a large retrospective cohort study of 13,981 patients with COVID-19 in Hubei Province in China, of which 1219 received statins [21]. They observed a significantly lower 28-day mortality in the group of statins (5.5 per cent mortality) than in the group not taking statins (6.8 per cent mortality, $P = 0.046$). Cox's study found that the risk of 28 days of mortality from all causes was 5.2% in the group of statins and 9.4% in the group that did not accept statins, with an adjusted risk ratio of 0.58. Patients taking statins also had lower levels of C-reactive protein and IL-6 [23, 28].

Daniels et al. recently published a retrospective single center study that examined all patients hospitalized at their center between February 10, 2020 and June 17, 2020 [30]. A total of 170 patients were diagnosed with SARS-CoV-2, of whom 53% developed a severe disease. It was noted that the use of statins prior to hospitalization was associated with a significantly lower risk of developing severe COVID disease (the adjusted odds ratio of 0.29, 95 confidence intervals from 0.11 to 0.71, $p < 0.01$). Statins have also been associated with faster recovery times in those who do not have a severe disease after control of comorbidity. The beneficial effect of using statins to reduce the risk of developing a severe disease was also observed in patients with negative COVID status in the hospital ($n=5281$), but this association was much weaker than in patients with coronavirus [28].

It can be concluded that those with a viral infection who received statins were much easier to carry pneumonia, despite the age and discharge from hospital was earlier by 3–4 days. Almost all patients were not affected by the cytokine storm.

■ CONCLUSIONS

This review, based on a sufficient number of studies, proves the effectiveness of statins through their pleiotropic and antihyphlimic actions against NAFLD/NASH-associated inflammation and fibrosis. Statins achieve this by acting on different target points, inhibiting RhoA and Ras, increasing PPAR α expression, lowering PON1 levels, preventing LSEC deduction and HSC activation, or allowing KC corona-like structures. Moreover, they also improve the adverse outcomes associated with NASH, such as MS, cardiovascular disease morbidity and mortality and hepato cellular carcinoma (HCC) prevention, are considered safe. These results of the study brought the drug closer to addressing the future use of statins as routine care in clinical practice at NAFLD/NASH. If confirmed by larger and longer-term clinical trials, statins may prove to be promising treatments for NASH, which remains an unresolved problem.

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