

Pleiotropic Effects of Statins in the of Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis

Agababyan Irina Rubenovna¹, Sadykova Shakhboza Shahobiddinovna²

¹Head of the Department of Therapy of the Faculty of Postgraduate Education of Samarkand State University

²Cardiologist, Samarkand City, Uzbekistan

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 pleiotropic 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 pleiotropic properties, which were observed in addition to the hypolipidemic effect. In various animal studies, statins have been found to reduce liver lipotoxic, 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 peroxisome proliferator-activated receptor alpha (PPAR α) and thus reducing mitochondrial and peroxisomal oxidation of fatty acids (FAO). Statins also increased paraoxonase1 (PON1), antioxidant, and antiatherogenic enzyme, which decreases with non-alcoholic fatty liver disease, as well as liver lipotoxic by separating cholesterol crystals and Kupfer cells (KC) from Crown-like structures (CLSs). 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 (CVD) 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 pleiotropic 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, Statins

1. Relevance

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 characterized 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 peroxidative 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 calorific 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, hypolipidemic drugs 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 paraoxonase1 (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 transformative growth factor beta 1 (TGF- β 1) [13]. In addition, statins reduce fibrogenesis in NASH by improving endothelial dysfunction with the recovery of sinusoidal liver space and stabilization of stellated 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 steatosis into NHA.

In addition, it has been reported that treatment with statins reduces the risk of atherosclerosis and mortality from CVS diseases associated with NAFLD. In other words, they are the only class of anti-hyperlipidemic agents that reduce CVS diseases at NAFLD [21]. Statins are generally considered to be anti-hyperlipidemic and their pleiotropic 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.

2. 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 infusion is facilitated by the interaction of the receptor-binding domain in 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, 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.

3. 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 proxy cytokines such as IL-6, IL-8 and chemotoxicity protein-1 monocytes, thereby altering the inflammatory path of damage to host cells [11,12,26].

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].

4. Influence on Expression Inhibitor ACE

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, 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 [31]. 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 [28,36].

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.

5. Conclusions

This review, based on a sufficient number of studies, proves the effectiveness of statins through their pleiotropic and hypolipidemic 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 liver sinusoidal endothelial cell dedifferentiation 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 hepatocellular 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.

REFERENCES

- [1] Younossi ZM, Marchesini G, Pinto-Cortez H, et al.: Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: implications for liver transplantation. *Transplantation*. 2019, 103: 22-27. 10.1097/TP.0000000000002484.
- [2] Agababayan I., Soliyeva S., Ismoilova Y. Condition of Coronary Arteries and Change of Lipid Profile in Coronary Heart Disease // *Annals of the Romanian Society for Cell Biology*. – 2021. – C. 207-213.
- [3] Alekshcheva, L. Z., Abdullaeva, M. A., Inoyatov, A. S., Jabborova, O. I., Nigmatullaeva, M. A., Kudratova, M. O., & Navruzova, U. O. (2021). Ways to solve the incidence of covid-19 as a global problem. *Annals of the Romanian Society for Cell Biology*, 25(4), 1873-1880. Retrieved from www.scopus.com.
- [4] Baran B, Akyüz F: Non-alcoholic fatty liver disease: what has changed in the treatment since the beginning?. *World J Gastroenterol*. 2014, 20:14219-29.
- [5] Dowman JK, Tomlinson JW, Newsome PN: Pathogenesis of non-alcoholic fatty liver disease. *QJM*. 2010, 103:71-83.
- [6] Lewis JR, Mohanty SR: Nonalcoholic fatty liver disease: a review and update. *Dig Dis Sci*. 2010, 55:560-578.
- [7] Ekstedt M, Hagstrom H, Nasr P, et al.: Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology*. 2015, 61: 1547-1554.
- [8] Younossi ZM, Stepanova M, Rafiq N, et al.: Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. *Hepatology*. 2011, 53:1874-1882.
- [9] Ikhtiyarova, G. A., Dustova, N. K., Khasanova M. A., Suleymanova G. S., & Davlatov, S. S. (2021). Pathomorphological changes of the placenta in pregnant women infected with coronavirus COVID-19. *International Journal of Pharmaceutical Research*, 13(1), 1935-1942. doi: 10.31838 /ijpr/2021.13.01.283
- [10] Agababayan I. R., Ruzieva A. A. Dynamics of the state of endothelial function in patients with CHF against the background of the main treatment // *Journal" Achievements of Science and Education*. – 2020. – №. 2. – C. 56.
- [11] Djordjevic DB, Zdravkovic M, Nagorni, et al.: A critical approach of guideline therapeutic recommendations for NAFLD. *Curr Vasc Pharmacol*. 2018, 16:228-238.
- [12] Oblokulov, A. R., & Niyozov, G. E. (2020). Clinical and epidemiological characteristics of patients with COVID-19. *International Journal of Pharmaceutical Research*, 12(4), 3749-3752. doi:10.31838/ijpr/2020.12.04.514.
- [13] Oblokulov, A. R., Husenova, Z. Z., & Ergashev, M. M. (2021). Procalcitonin as an indicator of antibacterial therapy in covid-19. *Annals of the Romanian Society for Cell Biology*, 25(3), 5220-5224. Retrieved from www.scopus.com
- [14] Park HS, Jang JE, Ko MS, et al.: Statins increase mitochondrial and peroxisomal fatty acid oxidation in the liver and prevent non-alcoholic steatohepatitis in mice. *Diabetes Metab J*. 2016, 40:376-385.
- [15] Yokohama K, Fukunishi S, Li M, et al.: Rosuvastatin as a potential preventive drug for the development of hepatocellular carcinoma associated with non-alcoholic fatty liver disease in mice. *Int J Mol Med*. 2016, 38:1499-1506.
- [16] Abraldes JG, Vilarrupla AR, Graupera M, et al.: Simvastatin treatment improves liver sinusoidal endothelial dysfunction in CCl4 cirrhotic rats. *J Hepatol*. 2007, 46:1040-1046.
- [17] Marrone G, Lucia R, Eugenio R, et al.: The transcription factor KLF2 mediates hepatic endothelial protection and paracrine endothelial-stellate cell deactivation induced by statins. *J Hepatol*. 2013, 58:98-103.
- [18] Rodríguez S, Raurell I, Arauz MT, et al.: A nitric oxide-donating statin decreases portal pressure with a better toxicity profile than conventional statins in cirrhotic rats. *Sci Rep*. 2017, 7:40461.
- [19] Schierwagen R, Maybüchen L, Hittatiya K, et al.: Statins improve NASH via inhibition of RhoA 2020 Ahsan et al. *Cureus* 12(9): e10446. DOI 10.7759/cureus.10446 16 of 17 and Ras. *Am J Physiol Gastrointest Liver Physiol*. 2016, 1:724-733.
- [20] Ioannou GN, Rooyen DMV, Savard C, et al.: Cholesterol-lowering drugs cause dissolution of cholesterol crystals and disperse Kupffer cell crown-like structures during resolution of NASH. *J Lipid*. 2015, 56:277-85.
- [21] Wang W, Zhao C, Zhou J, et al.: Simvastatin ameliorates liver fibrosis via mediating nitric oxide synthase in rats with non-alcoholic steatohepatitis-related liver fibrosis. *PLoS One*. 2013, 8:76538.
- [22] Iqbal U, Perumpail BJ, John N, et al.: Judicious use of lipid lowering agents in the management of NAFLD. *Diseases*. 2018, 6:87.
- [23] Musso G, Anty R, Petta S: Antioxidant therapy and drugs interfering with lipid metabolism: could they be effective in NAFLD patients?. *Curr Pharm Des*. 2013, 19:5297-313.
- [24] Milaciu MV, Vesa SC, Bocsan IC, et al.: Paraoxonase-1 serum concentration and PON1 gene polymorphisms: relationship with non-alcoholic fatty liver disease. *J Clin Med*. 2019, 8:2200.
- [25] Ioannou GN, Subramanian S, Chait A, et al.: Cholesterol crystallization within hepatocyte lipid droplets and its role in murine NASH. *J Lipid Res*. 2017, 58:1067-1079.
- [26] Musso G, Cassader M, Gambino R: Non-alcoholic steatohepatitis: emerging molecular target and therapeutic strategies. *Nat Rev Drug Discov*. 2016, 15:249-74.
- [27] Zhou Q, Liao JK: Pleiotropic effects of statins - basic research and clinical perspectives. *Circ J*. 2010, 74:818-26.
- [28] Yusufovna K. N. et al. Pharmacogenetics-A New Word in the Treatment of Rheumatoid Arthritis // *Annals of the Romanian Society for Cell Biology*. – 2021. – C. 259-265.
- [29] Kavalipati N, Shah J, Ramakrishnan A, et al.: Pleiotropic

- effects of the statins. *Indian J Endocrinol Metab.* 2015, 19:554-62.
- [29] Bravo M, Raurell I, Hide D, et al.: Restoration of liver sinusoidal cell phenotypes by statins improves portal hypertension and histology in rats with NASH. *Sci Rep.* 2019, 9:20183.
- [30] Athyros VG, Boutari C, Stavropoulos K, et al.: Statins: an under-appreciated asset for the prevention and the treatment of NAFLD or NASH and the related cardiovascular risk. *Curr Vasc Pharmacol.* 2018, 16:246-253.
- [31] Idiev O. E. Evaluation of Electromyographic studies of masticatory muscles in Children with Cerebral Palsy. – 2021. –P. 46-48.
- [32] Idiev O. E. Morpho-functional state of the maxillofacial region in children with cerebral palsy // *Middle European Scientific Bulletin.* – 2020. – T. 7. – P. 47-50.
- [33] Bril F, Sanchez PP, Lomonaco R, et al.: Liver safety of statins in prediabetes or T2DM and nonalcoholic steatohepatitis: post hoc analysis of a randomized trial. *J Clin Endocrinol Metab.* 2017, 102:2950-296.
- [34] Eslami L, Merat S, Malekzadeh R, et al.: Statins for non-alcoholic fatty liver disease and nonalcoholic steatohepatitis. *Cochrane Database Syst Rev.* 2013, 12:8623.