ISSN 2231-2218

ASIAN JOURNAL OF PHARMACEUTICAL AND BIOLOGICAL RESEARCH

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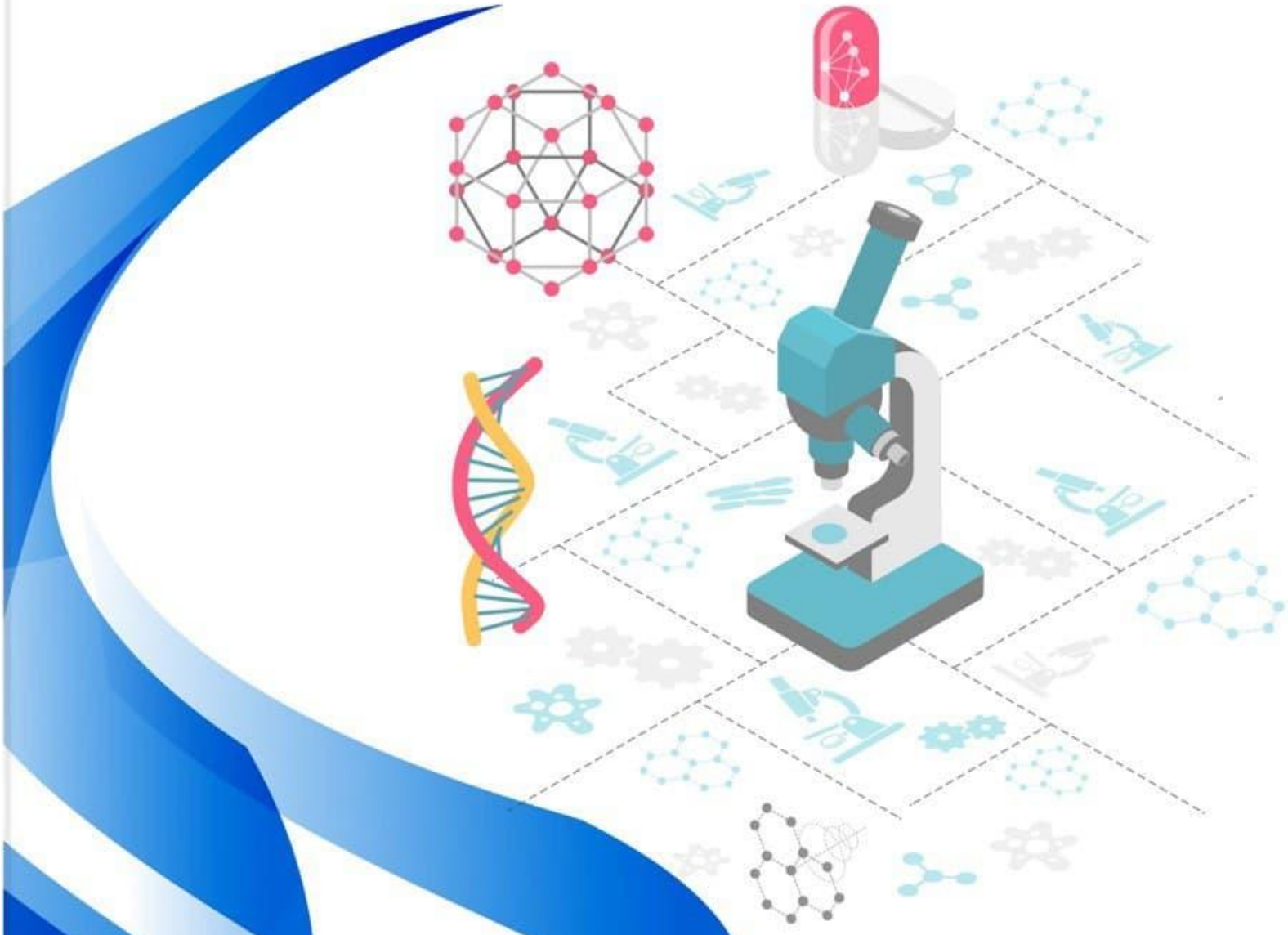

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Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
researchbib 8
Volume 13 Issue 3
SEPT.-DEC. 2024

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Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
researchbib 8
Volume 13 Issue 3
SEPT.-DEC. 2024

CORONAVIRUS INFECTION AND DYSLIPIDEMIA — IS THERE A CONNECTION?

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Abstract. Dyslipidemia is one of the most common concomitant conditions in patients infected with the SARS—CoV-2 coronavirus. Based on the analysis of current literature, the review evaluates the possible effect of dyslipidemia on the course of the disease and prognosis in patients with coronavirus infection (COVID-19), as well as the effect of virus infection on the lipid profile in patients with dyslipidemia. The inflammatory process in COVID-19 leads to an increase in the concentration of high-density lipoproteins (HDL), modulation of apolipoproteins, an increase in serum concentration of amyloid protein A and a decrease in the content of apolipoproteins A-I, M and E, which has a negative effect on the antioxidant, anti-inflammatory and immunomodulatory role of HDL. The use of statins in patients with COVID-19 may help reduce the risk of lipid metabolism disorders. By reducing the synthesis of endogenous cholesterol, statins reduce its amount in lipid rafts, which can limit the penetration of SARS-CoV-2 into host cells. In addition, statins, by reducing the overexpression of proinflammatory cytokines, reduce the intensity of the "cytokine storm" accompanying COVID-19.

Keywords: COVID-19, dyslipidemia, obesity, treatment, lipoproteins, statins, fibrates.

Introduction. Dyslipidemia occurs in 30-60% of the population [1]. Dyslipidemia is one of the most common concomitant pathological conditions among patients infected with the SARS-CoV-2 coronavirus. Moreover, in patients with dyslipidemia, the metabolic and lipid profile could deteriorate during the coronavirus pandemic (COVID-19) due to decreased physical activity and an unbalanced diet during self-isolation, creating an unfavorable background for infection with SARS-CoV-2 coronavirus [2]. Currently, the study of the possible effect of dyslipidemia on the severity and prognosis in patients with COVID-19 remains relevant.

Objective: based on the analysis of modern literature, to evaluate the possible effect of dyslipidemia on the severity and prognosis in patients with COVID-19, as well as the effect of infection with SARS-CoV-2 coronavirus on lipid metabolism in patients with dyslipidemia.

The effect of obesity on the course of COVID-19

Obese people turned out to be one of the most vulnerable categories of patients during the COVID-19 pandemic. An increased body mass index (BMI) is an independent risk factor for severe COVID-19. The results of the meta-analysis showed that the risk of an adverse outcome of COVID-19 increases by 5% with an increase in BMI by 5 kg/m2 [3]. Obese individuals have an increased risk of dyslipidemia, insulin resistance, diabetes mellitus, hypertension, cardiovascular and cerebrovascular diseases, which are known as predictors of poor prognosis in SARS-

CoV infection [4]. A sedentary lifestyle in people with obesity and dyslipidemia during a pandemic contributes to a decrease in immune protection and an increased risk of infection with the SARS-CoV-2 coronavirus [5]. The control of plasma lipids and lipoproteins, such as low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), high-density lipoproteins (HDL) and triglycerides (TG), is of great importance in managing the risk of cardiovascular diseases (CVD) [2].

The role of lipids in the immune response

The severe course of COVID-19 is often accompanied by excessive activation of the immune system, leading to various complications such as respiratory failure, multiple organ dysfunction, coagulopathy, and ultimately death [6]. Tissue damage caused by viral infection promotes the release of pro-inflammatory cytokines, including interleukin 6 (IL-6), inflammatory macrophage proteins and monocytic chemoattractant protein 1, which leads to additional involvement of protective cells such as neutrophils, macrophages and T cells. Activation of these cells causes uncontrolled, persistent inflammation and impaired immunity with further accumulation of eicosanoids, including thromboxane B2, prostaglandin E2, leukotriene B4 and lipoxin A4, causing the development of hypercoagulation in patients with COVID-19, which can contribute to the development of life-threatening complications and lead to death [7].

Ongoing inflammatory processes lead to an increase in HDL content, modulation of apolipoproteins, an increase in serum concentration of amyloid protein A and a decrease in the content of apolipoproteins A-I, M and E. These effects have a negative effect on the antioxidant, anti-inflammatory and immunomodulatory role of HDL [7]. HDL is known to stimulate the reversal of cholesterol due to transport from the peripheral parts to the liver, and also participate in the modulation of the immune system and increase anti-infective protection [7]. In addition to the antioxidant, antithrombotic and immunomodulatory effects, HDL plays a role in binding and neutralizing lipids associated with pathogens and mediating a hyperstimulated immune response in sepsis [8]. The antioxidant and anti-inflammatory properties of HDL are markedly reduced when infected with influenza viruses and human immunodeficiency [9, 10]. The inflammatory process is accompanied by a change in the HDL apolipoprotein, but the exact mechanism of this phenomenon is currently unknown [11]. An imbalance in the antioxidant mechanism leads to the formation of oxidized HDL, which accompany the process of active inflammation and oxidative stress. Inactivation of the paraoxonase 1 (PON1) enzyme in HDL serves as an additional stimulus to the lipid oxidation process, which further impairs HDL function [7]. It has been shown that low PON1 activity is associated with a poor prognosis in patients with CVD, and the activity of this enzyme is significantly reduced in various inflammatory and infectious diseases [12].

Excessive accumulation of oxidized HDL and LDL leads to activation of the type 1 lectin-like receptor transporter, which stimulates further inflammatory processes that exacerbate tissue damage. This leads to changes in lipoprotein

transport and to inadequate interaction of apolipoprotein A-I and the A1 cassette transporter binding adenosine triphosphate. As a result, the processes of cholesterol esterification by lecithin cholesterol acyltransferase are inhibited, which reduces the return of cholesterol esters to the liver immediately after interaction with the liver transporter OATP1B1 [12]. As a result, VLDL and TG accumulate [7]. Against the background of hypercholesterolemia, cholesterol accumulates in macrophages and other cells of the immune system, stimulating inflammatory reactions, including strengthening of the Toll-like receptor. LDL is known to serve as the main transporter of cholesterol and phospholipids in the circulatory system, and in acute inflammation, LDL and apolipoproteins B are oxidized to oxidized LDL [13]. The process of LDL accumulation promotes the formation of cholesterol crystals in macrophages and stimulates the activation of the inflammasome, which leads to the release of pro-inflammatory cytokines such as interleukin (IL) 1B and IL-18, exacerbating inflammation in damaged tissues [14]. High levels of LDL and TG in serum also lead to endothelial dysfunction, contributing to the development of complications associated with CVD, which can increase mortality in COVID-19 [7]. In addition, CVD risk factors such as dyslipidemia, in particular the accumulation of oxidized LDL, cause immune restructuring in myeloid cells, which predisposes to exaggerated inflammatory reactions after infection, in particular the SARS-CoV-2 coronavirus [15].

In a study involving 1,411 patients with COVID-19, the expediency of assessing the content of total serum cholesterol, LDL, HDL cholesterol and TG was evaluated to predict the course of COVID-19 [16]. It was found that low HDL and high TG levels, measured before or during hospitalization, were significant predictors of severe COVID-19. The researchers point out that the lipid profile serves as a sensitive marker of inflammation and it must be taken into account [16]. In another study, it was shown that a three-fold or more increase in the plasma atherogenicity index became a predictor of inpatient mortality among patients with COVID-19 and an early biomarker of severe disease [17].

Statins: a place in the treatment of patients with COVID-19 and dyslipidemia

The effect of taking statins on the severity and prognosis of COVID-19 is the subject of close study. In general, the results of a meta-analysis of the effectiveness of statins in COVID-19 are contradictory. The ambiguous results are probably related to the impact of a number of factors, such as age, gender, concomitant diseases, polypragmasia, genetic predisposition, environmental factors, lifestyle, etc. [18]. An important factor that could explain the contradictions in the meta-analysis results may be the use of different statins. In a study by R. Rossi et al. [19] It was shown that the mortality of patients with COVID-19 taking simvastatin and atorvastatin decreased, while the mortality of patients receiving pravastatin and rosuvastatin did not change. A study by V. Cariou et al. [20] demonstrates that the effect of statins may depend on the presence, stage and severity of CVD in patients with COVID-19. To date, it is known that previously prescribed statin treatment cannot be discontinued in patients

infected with the SARS-CoV-2 coronavirus [21]. However, the results presented in meta-analyses should be interpreted cautiously, since this type of research is associated with a number of errors [22]. In addition, the methodology of some meta-analyses is controversial [23, 24]. Future studies need to provide more information about the possible benefits of statin treatment in patients with COVID-19.

It is known that a decrease in cholesterol in patients with COVID-19 was accompanied by a significant decrease in the amount of viral mRNA inside the cell, which further confirms the role of cholesterol in the pathogenesis of the disease [25]. Simultaneously with a decrease in the synthesis of endogenous cholesterol under the action of statins, its amount in lipid rafts decreases, which may limit the penetration of SARS-CoV-2 coronavirus into body cells [26].

Inhibition of SARS-CoV-2 coronavirus replication is one of the direct mechanisms of action of statins. The high affinity of pitavastatin, rosuvastatin, lovastatin and fluvastatin to the main protease of the SARS-CoV-2 coronavirus (Mpro), which is involved in the regulation of viral replication and transcription, has been shown [27]. In one of the studies, it was demonstrated (by modeling molecular dynamics) that pitavastatin binds strongly to the active center of the SARS-CoV-2 coronavirus polymerase responsible for viral RNA replication. Based on the data obtained, the authors indicate that this mechanism can be used to treat COVID-19 [28]. Thus, statins can have a direct inhibitory effect on the penetration of the SARS-CoV-2 coronavirus into the cell and its replication, however, the mechanisms presented require confirmation in in vitro studies.

In addition to the direct effect on the SARS-CoV-2 coronavirus, statins may have an indirect effect on the course of COVID-19. Statins, contributing to a decrease in the overexpression of proinflammatory cytokines, reduce the intensity of the "cytokine storm" accompanying COVID-19 [29]. The level of IL-6, one of the key pro-inflammatory cytokines involved in the "cytokine storm", positively correlates with the severity of COVID-19 [29]. The high content of IL-6 in serum contributes to the development of a "cytokine storm", and can also trigger macrophage activation syndrome with the development of severe inflammation manifested by fever, hyperferritinemia, hypofibrinogenemia, coagulopathy and cytopenia [30]. In previous studies, statins have been shown to reduce serum IL-6 levels. A meta-analysis of 19 randomized clinical trials (RCTs), including 6214 patients with heart failure, showed that statin intake was accompanied by a decrease in serum levels of both IL-6 and C-reactive protein. The effect of lipophilic statins (atorvastatin, simvastatin and pitavastatin) was more pronounced [31]. The mechanism of action of statins, as a result of which the IL-6 content decreases, is complex and consists in inhibition of Toll-like receptor 4 (TLR 4), which has an anti-inflammatory effect through the nuclear factor kappa B [32]. In an experimental study on mouse cells, it was shown that atorvastatin reduces the expression of the TLR 4 gene [33].

Currently, it is known that the vascular endothelium is significantly damaged during COVID-19, therefore, the effect of statins on the vascular endothelium is of

interest. Statins have been shown to protect the vascular endothelium from the effects of free radicals [32], and also contribute to a decrease in the proinflammatory activity of NOD-like receptors and the pyrin domain containing 3 inflammasomes (NLRP3) [34]. In addition, while taking statins, the regenerative ability of the vascular endothelium is activated due to an increase in the number of endothelial progenitor cells [35].

The anticoagulant properties of statins should be noted. Thromboembolic complications are common in patients with COVID-19. In a multicenter retrospective study, the overall rate of thrombotic complications associated with COVID-19 was 9.5% (95% CI 6.8–12.8) [36]. Previous studies have shown that the use of statins (especially atorvastatin and rosuvastatin) reduces the risk of recurrent pulmonary embolism, one of the most severe thromboembolic diseases [37]. These beneficial effects of statins are related to their effect on the inhibitor of plasminogen activator 1. A meta-analysis of 16 RCTs showed that statins (especially atorvastatin) significantly reduced the content of plasminogen activator inhibitor 1 in serum, which increased the degradation of fibrin clots by plasmin [38]. Statins have also been shown to have an anticoagulant effect, reducing the content of von Willebrand factor antigen in plasma [39].

The antifibrotic effect of statins is of particular interest from the point of view of complications of SARS-CoV-2 infection (especially in long-term postcovid syndrome). In a study involving 107 patients with COVID-19, it was shown that 3-6 months after recovery, some of them developed pulmonary fibrosis [40]. In an experiment using mice and human lung fibroblasts/ myofibroblasts, the effect of atorvastatin on the development of fibrosis was evaluated. It has been shown that the administration of atorvastatin to mice leads to a decrease in the degree of fibrosis and collagen accumulation in interstitial tissue, and also contributes to a decrease in the concentration of alpha-smooth muscle actin (α-SMA) and lysyl oxidase-like protein 2 [41]. In vitro studies have shown a decrease in the content of α-SMA and fibronectin due to the restriction of the activity of transforming growth factor β (TGF-β) [41]. It has also been suggested that statins contribute to the inhibition of the epithelial-mesenchymal transition, thereby weakening the transmission of TGF-β signals, reducing the intensity of connective tissue remodeling [42]. Statins also enhance fibroblast apoptosis [43].

It should be noted that statins, by increasing the content of HDL, have an antiviral effect. It has been shown that HDL can bind lipopolysaccharide, as well as lipoteichoic acid [44], block the penetration of a number of viruses into cells, reducing their infection and the possibility of virus replication in various tissues [45]. In addition, HDL is characterized by antioxidant, anticoagulant properties, has immunomodulatory and anti-inflammatory properties, and is also involved in the regeneration of vascular endothelium [46]. The observed decrease in HDL content by 40-70% in infectious diseases, including COVID-19, can worsen the course of the disease [46].

Statins, affecting the level of arachidonic acid, have an indirect antiviral effect. In a review article, it was shown that the risk of developing COVID-19 is higher with arachidonic acid deficiency [47], and statins significantly increase its plasma concentration in patients with hypercholesterolemia [48]. In one in vitro study, the effect of omega-3 polyunsaturated fatty acids (including arachidonic acid) on the penetration of the SARS-CoV-2 coronavirus into the cell was evaluated. At the same time, it was demonstrated that these fatty acids prevent the binding of the virus to angiotensin converting enzyme 2 on the cell surface [49]. Thus, statins, by increasing the synthesis of arachidonic acid, can prevent the infection of cells with the SARS-CoV-2 coronavirus.

The use of fibrates in patients with COVID-19

Fibrates are assigned an important place in the treatment of patients with COVID-19 with an increase in TG levels. A clinical case of severe hypertriglyceridemia due to a temporary decrease in lipoprotein lipase activity in COVID-19 disease in a 45-year-old woman is described. The patient's lipoprotein lipase activity was reduced and recovered only to 20% of normal values 5 months after the COVID-19 infection. Fibrate treatment and a strict lipid-lowering diet were accompanied by an improvement in the patient's condition and a decrease in TG content to normal values [50].

Conclusion

The risk of severe COVID-19 is higher in cases of lipid metabolism disorders. At the same time, infection with the SARS-CoV-2 coronavirus contributes to lipid metabolism disorders, affecting mainly HDL metabolism. The use of statins in patients with COVID-19 may reduce the risk of severe disease and death. Statins, due to their pleiotropic mechanism of action, reduce the likelihood of SARS-CoV-2 coronavirus entering the cell and reduce the risk of complications of a "cytokine storm" [51]. The risk of severe COVID-19 is higher in patients with familial hypercholesterolemia, high and very high risk of CVD. In these patients, lipid metabolism parameters should be especially carefully monitored and lipid-lowering treatment should be planned. In cases of hypertriglyceridemia due to a temporary decrease in lipoprotein lipase activity in COVID-19 disease, the appointment of fibrates and adherence to a strict lipid-lowering diet will improve the prognosis and reduce blood TG levels.

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