

The Toxicity and Biological Functions of Statins During Treatments

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Abstract. Cardiovascular morbidity and mortality are reduced by statins, which are drugs that lower cholesterol and reduce LDL-c. Statins function by competitively blocking the primary rate-limiting enzyme in HMG-CoA reductase, inhibiting it so that no substrate can enter and no HMG-CoA can be converted to mevalonic acid. Statins are by far the mainstay of majority and minority prevention of atherosclerotic cardiovascular disease, but they have also been linked to a variety of side effects. Statin therapy should be discontinued because of muscle symptoms associated with it and the development of new-onset type 2 diabetes as a side effect of statins is a serious issue and the pathogenesis of it is still unclear. This paper focuses on the biological function of statins and their toxicity, i.e. the mechanisms responsible for the adverse effects. It is intended to inform the study of the mechanisms of toxicity episodes of statins. Some of the mechanisms of toxicity onset of statins cannot be determined at this time, various patient populations could be studied in future studies to explore the side effects of statins.

Keywords: Statins; toxicity; biological functions; CVDs.

1. Introduction

Cardiovascular diseases (CVDs) are major reason for global mortality and disability, it is affecting people's lives. Thirty-one percent of global deaths are attributed to cardiovascular disease. On account of the complexity and severity of these diseases, treatment and recovery is difficult, and other complications may occur during treatment of CVDs. Coronary heart disease, as a kind of cardiovascular disease, belongs to ischemic heart disease. It is characterized by atherosclerosis of the coronary arteries causing narrowing or occlusion of the lumen, leading to myocardial ischemia, hypoxia, or necrosis and discomfort such as chest tightness and chest pain.

In recent years, the incidence of coronary heart disease has been a younger trend. Coronary heart disease is mainly divided into chronic coronary artery disease and acute coronary syndrome. As research progresses, there are more profound factors that influence the development of coronary heart disease, such as sleep apnea, elevated levels of high-sensitivity c-reactive protein, high triglycerides, homocysteine, preeclampsia, and autoimmune diseases. Some drugs used in cardiology have additional pharmacological effects that go beyond the primary therapeutic target. Human metabolism has significant influence on most cardiovascular diseases. However, the patient's cell metabolism will be affected by the drugs. Statins play a major role in treatment of coronary heart diseases. The critical step that statins restrain cholesterol is that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) is turned into mevalonate by the enzyme HMG-CoA reductase. Statins have effects that extend beyond their cholesterol-lowering qualities due to the mevalonate pathway's impact on endothelial function, inflammatory response, and coagulation. The liver's cholesterol production is reduced, which generates an augment in the expression of the LDL receptor on the cell envelope and the production of microsomal HMG-CoA reductase. Taking statin therapy every year reduces the risk of vascular disease, as it turns out. Myopathy (defined as muscle pain or weakness combined with a large increase in creatine kinase blood concentration), new-onset diabetes, and possibly hemorrhagic stroke are among the serious adverse events that can occur due to long-term statin therapy, which are adverse reactions to statins. The theory behind statin toxicity is that HMG-CoA reductase is inhibited. In addition to myopathy, statins can have neurological effects. The spectrum of diseases that can occur after a hemorrhagic stroke is characterized by cognitive decline, peripheral neuropathy, depression,

confusion, memory loss, and personality changes. A population-based cohort study found that patients on statin therapy with a longer exposure period and the risk of developing dementia was lower with high-potency lipophilic statins [1].

The development of statin toxicity has been suggested by multiple mechanisms, but the disease is still difficult to identify due to the absence of clear definitions and biomarkers. More investigation into this matter is necessary given the extensive use of statins in majority and minority prevention to lower cholesterol and subsequently cardiovascular morbidity and mortality. Amphetamine is one possible new therapy option. Reducing LDL-c in individuals who are intolerant to statins has been demonstrated. The CLEAR Outcome trial is now looking into the consequence of this medication on major cardiovascular events in people with statin-intolerance who have or have a high risk of cardiovascular disease. Numerous scientific and clinical studies have demonstrated the potential side effects of statins. The objective of this investigation is to review the pertinent mechanism of action and toxicity of statins.

2. Biological Functions of Statins

2.1. Cardiovascular Disease, Blood Lipids and Diabetes

Statins are the cornerstone of drug therapy to prevent atherosclerotic cardiovascular disease. Statins are a kind of reductase inhibitors. It can reduce the cholesterol level in the serum, liver and aorta. Statins are also mainly used to decrease very low-density lipoprotein cholesterol, LDL cholesterol levels. Statins can regulate blood lipids, the LDL-c can be significantly reduced, and because the affinity of statins and HMG-CoA reductase is thousands of times higher than the affinity of HMG-CoA and its reductase, competitive inhibition of HMG-CoA reductase occurs, restraining the synthesis of cholesterol. For the moment, the major toxicity that statins show is myotoxicity and hepatic adverse reaction. In accordance to some study findings, statins may minimize oxidative stress, reductions in thrombosis and inflammation, improvement in endothelial function, and improve vascular tone [2]. On the other hand, certain investigations have come across potentially hazardous pleiotropic effects that include diabetes, hemorrhagic stroke, liver disease, and cognitive decline as well as to a threat of muscle-related side effects.

2.2. Cancer and other types of diseases

Statins have also shown great potential in the prophylaxis and cure of cancer. The direct impact of statins on cells and tumours has been shown in laboratory experiments, and this action can improve the response to immunotherapy, targeted medications, chemotherapy, and radiation therapy. One prevalent cancer is head and neck cancer (HNC), and lipophilic statins can be potent drugs for head and neck cancer because they preserve normal tissue during treatment and enhance the sensitivity of HNC to radiation and other routine therapies. Cholesterol is crucial for the maintenance of cell membranes as part of biochemical processes, steroid hormone synthesis, vitamin D and lipid rafts and caveolae form during bile acid production, which helps with convey, cellular signal transduction and cell polarization. Statins affect isoprenoid biosynthesis in ways that can have multiple pleiotropic effects, furthermore. Cell growth, survival, and differentiation are dependent upon intracellular signaling proteins like Ras, Rac, and Rho are lipid anchors for isoprenoids. Statins' therapeutic efficacy may be enhanced by regulating isoprenylation, which can affect cellular signaling transduction [3,4]. Inhibiting hepatic cholesterol biosynthesis is more effectively achieved by hydrophilic statins like pravastatin and rosuvastatin than lipophilic statins like simvastatin and lovastatin. Atorvastatin is more readily available in the peripheral area and can affect multiple mevalonate metabolism targets in cancer cells [5,6]. Lowering serum cholesterol levels and preventing cardiovascular disease is achieved by using Simvastatin, which is a semi-synthetic derivative of lovastatin [7]. Any large study of cancer patients will often find that lipophilic statins are used incidentally.

3. Toxicity

3.1. Myotoxicity of Statins

The rate of myopathy caused by statin is between 7% and 29% [8]. Sabine, Niklas and Zhaokang et al [9]. used human and rodent muscles to investigate the mechanism by which statins induce myopathy. That is, statins can make skeletal muscle more vulnerable to myopathy during the treatment of patients: FKBP12 was discovered in the ryanodine receptor 1 (RyR1) release channel of the sarcoplasmic reticulum (SR) Calcium (Ca^{2+}), and is accompanied by a large amount of spontaneous Ca^{2+} release. Statin therapy caused FKBP2 to dissociate from RyR1, leading to Ca^{2+} leakage that was dependent on reacting nitrogen and responsive oxygen species (RNS/ROS). Muscle dysfunction, including heart failure and muscular atrophy, has been linked to the instability of RyR1 [10-12]. The spontaneous release of Ca^{2+} from SR occurs when FKBP12 dissociates from RyR1.

Protein retrogradation and routinization of cell death are facilitated by this process.

The myopathic mechanism of Ca^{2+} leaks, known as Ca^{2+} sparks (elementary Ca^{2+} release events from clusters of RyR1), is shared by amount of skeletal and muscle diseases, such as sarcosus dystrophy and malignant hyperthermia [10,13]. In order to determine how statins affected SR Ca^{2+} leakage in intact muscle fibres, the researchers examined the effect on the latter. They found that in statin-treated rats' muscle fibres, sparks occurred more frequently, took longer, and had a larger amplitude, all of which increased the mass of the sparks and Ca^{2+} leakage from the sparks' borrowed pathways.

There are several symptoms that can be present, including myalgia with ordinary creatine kinase (CK) values or asymptomatic hyperCK-emia, as well as potentially fatal rhabdomyolysis and necrotizing autoimmune myopathy, are associated with statin-associated muscle symptoms (SAMS). Most frequently, myalgia with increased CK is present. Myopathy brought on by statins manifests clinically as lethargy, cramping at night, muscle soreness, sensitivity, and tendon discomfort.

3.2. Hepatotoxicity of Statins

Mitochondrial dysfunction is the main mechanism of hepatotoxicity induced by statins. After statin treatment, superoxide levels in mitochondria increased significantly. An increase in superoxide can lead to mitochondrial dysfunction. In addition, another main reason for hepatotoxicity lured by statins is that they result in apoptosis of cells. Hepatotoxicity may be induced by the inhibition of mitochondrial membrane depolarization, electrotransport chain complexes (I and III), and calcium release. Mitochondrial metabolism, which is dependent on CYP450, is a system for producing ROS and is involved in the cell death process. Lipid peroxidation is caused by liver cells producing large amounts of ROS during statin use, resulting in a decline in mitochondrial membrane latent and promotes cytotoxicity [14,15].

Hepatocellular and cholestatic forms of injury have both been linked to statin-induced liver injury. A main increase in alanine aminotransferase (ALT) is indicative of hepatocellular pattern liver injury, while an increase in bilirubin and alkaline phosphatase (ALP) is linked to cholestatic pattern liver injury [7,8]. Hepatocellular damage linked to statins often happens five to ninety days after treatment starts [16,17]. 10% of people who have bilirubin levels more than twice the ULN will die from severe hepatic liver damage [18].

3.3. Mechanism of T2D induced by Statins

Despite the fact that many large clinical trials have documented the beneficial effects of statins in primary and secondary prevention, there is speculation that statins could lead to the development of new-onset diabetes. The development of atherosclerotic cardiovascular disease can be attributed to type 2 diabetes, and recent findings suggest that statins elevate the risk of developing diabetes by 9%-12% over the course of treatment. During treatment, statins impair organ sensitivity to insulin and inhibit insulin secretion. Gene variations in the LDL cholesterol-lowering medicines' target genes

may contribute to the increased risk of type 2 diabetes. Type 2 diabetes is characterised by both IR and impaired insulin production, with statin-induced diabetes mostly resulting from decreased insulin secretion. A number of transcription factors that are important in controlling β -cell activity and the development of β -cells into insulin-producing cells also regulate the release of insulin in β -cells [19,20]. 3-hydroxy-3-methylglutamyl coenzyme is an enzyme. The risk of T2D is increased by a reductase (HMGCR). Takei et al [21] use of Cre-loxP technology allowed for the β -cell-specific deletion of Hmgcr in mice. Because of decreased β -cell mass and insulin production, experimental subjects missing Hmgcr in β -cells showed low insulin concentrations and hyperglycemia. Impaired β -cell proliferation is the primary cause of reduced β -cell bulk. The researchers came to the conclusion that HMGCR is essential for both the growth of β -cells and insulin production. These results highlight the role of the mevalonate in β -cell formation. The researchers came to the conclusion that HMGCR is essential for both the growth of β -cells and insulin production. These results highlight the role that the mevalonate pathway plays in maintaining glucose homeostasis and β -cell function. Statins enter the liver through the OATP1B1 transport protein. Statins block HGM-CoA in the liver, which causes the methylcarbamate pathway to be downregulated, low-density cholesterol receptor (LDLR) expression to increase, and LDL-C concentrations to rise. Excessive LDL-C levels are harmful to pancreatic β -cells, resulting in decreased insulin production and, eventually, hyperglycemia and type 2 diabetes.

4. Conclusion

This paper analyzes the function of statins on cancer, cardiovascular disease, lipids and diabetes, and reveals the mechanisms by which statins cause myopathy, hepatotoxicity and type 2 diabetes. The main purpose of analyzing such issues is to provide some ideas on the discontinuation and continued use of clinical statins in the future. Statins are widely used to lower cholesterol and have been shown to significantly decrease cardiovascular incidence and death rate. The toxicity of statins deserves further study, both in primary and secondary prevention. The more familiar one is with the mechanisms of statins, the lower the chance of clinical complications. What has not been established in this paper is a clear mechanism of statin-induced nephrotoxicity, as the effects of statin-induced nephrotoxicity are small, but not negligible. Phenylalanine is a new therapeutic option currently under development. Lowering LDL-c levels has been shown to occur in patients who are intolerant to statins. This drug's impact on major cardiovascular events is being investigated by researchers in sufferers who are both statin-tolerant and at high-stake for cardiovascular disease. If statins are effective in increasing the therapeutic efficacy of head and neck radiation for diseases like head and neck cancer, they may be the most important factor in minimising the tenotoxic chemotherapy is necessary to improve treatment outcomes and act as a radiosensitizer.

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