Potential Benefits and Risks of Statins

Subjects: Physiology

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HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors, commonly known as statins, are the primary treatment choice for cardiovascular diseases, which stand as the leading global cause of mortality. Statins also offer various pleiotropic effects, including improved endothelial function, anti-inflammatory properties, reduced oxidative stress, anti-thrombotic effects, and the stabilization of atherosclerotic plaques. However, the usage of statins can be accompanied by a range of adverse effects, such as the development of type 2 diabetes mellitus, muscular symptoms, liver toxicity, kidney diseases, cataracts, hemorrhagic strokes, and psychiatric complications. These issues are referred to as statin-associated symptoms (SAS) and are relatively infrequent in clinical trials, making it challenging to attribute them to statin use definitively. Therefore, these symptoms can lead to significant problems, necessitating dose adjustments or discontinuation of statin therapy.

Keywords: statin ; pleiotropic effects ; statin-associated symptoms

1. Introduction

According to statistics provided by the World Health Organization (WHO), cardiovascular disease (CVD) was the primary cause of death on a global scale in 2019, accounting for 32% of all fatalities [1]. Data collected from 2015 to 2018 indicates that 38.1% of adults in the United States, equivalent to 93.9 million individuals, had total cholesterol levels equal to or exceeding 200 mg/dL [2]. Furthermore, elevated levels of low-density lipoprotein cholesterol were responsible for 4.51 million deaths worldwide in 2020, indicating a 19% increase compared with 2010 [3]. Increased levels of low-density lipoprotein (LDL) lead to a condition called atherosclerosis, where excessive cholesterol accumulates in various arteries throughout the body. The buildup of LDL in the coronary vessels and carotid arteries increases the risk of experiencing a myocardial infarction or stroke [4][5][6].

Atherosclerosis is no longer limited to Western countries. It has become a global health concern, affecting younger individuals, a wider range of ethnic backgrounds, and more women [7]. Statins have served as the primary treatment for preventing CVDs for many years, starting with the introduction of lovastatin in 1987, which was the first statin available for commercial use [8]. These medications work by competitively inhibiting HMG-CoA reductase, a crucial enzyme that controls the rate of cholesterol production in the liver. This inhibition leads to a decrease in cholesterol synthesis within the liver. In response to the lowered cholesterol, hepatocytes increase the production of LDL receptors, enhancing the uptake and recycling of LDL cholesterol. Consequently, this process results in reduced levels of LDL cholesterol in the bloodstream. This reduction in serum LDL levels is the primary mechanism through which statin therapy decreases the risk of cardiovascular problems and improves overall outcomes [9][10].

Statins can be categorized into different classes based on either their origin or chemical structure. Regarding their origin, there are three classes: natural, semi-synthetic, and synthetic. Natural statins are derived from the fermentation of fungi and encompass lovastatin and pravastatin [11]. Semi-synthetic statins, such as simvastatin, are produced through a process that involves modifying lovastatin, specifically by substituting the 2-methylbutyrate group at the C-8 position of the naphthalene ring with 2,2-dimethylbutyrate [12]. Synthetic statins are chemically synthesized and share only the common dihydroxyheptanoic acid pharmacophore (resembling HMG-CoA) that mimics the HMG-CoA substrate in binding to HMGR [13]. Examples of synthetic statins include atorvastatin, cerivastatin, rosuvastatin, fluvastatin, and pitavastatin. All forms of statins can undergo reversible metabolism through lactonization [14].

In general, statins are considered safe and well-tolerated medications, and they are the most commonly prescribed drugs worldwide. Clinical trials have shown that statins effectively lower LDL cholesterol levels and improve patient prognosis without increasing complications [15]. These drugs also have additional benefits, such as reducing inflammation markers such as C-reactive protein and pro-inflammatory cytokines. Statins improve endothelial function in patients with cardiovascular risk factors and are associated with protective effects in coronary artery disease (CAD) [16][17]. They also play a role in preventing stroke, improving outcomes in acute coronary syndrome, reducing the risk of atrial fibrillation after

heart surgery, and benefiting patients with heart failure. Statin treatment has demonstrated cardiovascular risk reduction, even in healthy individuals with elevated inflammation markers [18][19].

In addition to their positive impact on vascular health, many studies have highlighted the potential pleiotropic effects of statins that could affect various tissues and organs. Although most patients can address adverse effects by trying a different statin or adjusting the treatment plan, such as reducing the dosage or combining statins with non-statin drugs, current guidelines favor the term “statin-associated side effects” over “statin intolerance”. Evaluating and addressing these adverse effects can be challenging, even though they occur infrequently in clinical studies. The most common of these are statin-associated muscle symptoms (SAMS), typically characterized by subjective muscle pain and are observed in approximately 5% to 20% of patients. In some susceptible individuals, statins slightly elevated the risk of developing diabetes mellitus [20]. The risk of significant liver damage induced by statins is extremely low, estimated at around 0.001%.

Some individuals fail to achieve the desired LDL-C target levels or encounter challenges in tolerating statins, especially when on high doses for extended periods. The future focus on reducing the burden of CVD involves combining statins with diverse therapeutic approaches and exploring new drugs [21]. In recent times, there has been significant progress in the development and approval of various cholesterol-lowering medications, expanding the range of pharmacological options beyond statins. Emerging agents such as PCSK9 inhibitors, bempedoic acid, inclisiran, ANGPTL3 inhibitors, PPARβ/δ agonists, and LXR agonists show promise in effectively reducing LDL-C levels, demonstrating encouraging positive outcomes [22].

2. Pleiotropic Benefits of Statin

2.1. Enhancing Endothelial Function

The onset of atherosclerosis often involves endothelial dysfunction, which is influenced by established cardiovascular risk factors such as hypertension, smoking, and high blood sugar levels. These factors, mediated by nitric oxide (NO), can interfere with the regular vasodilation process. Statins play a role in inhibiting the prenylation of Rac and Rho proteins, leading to an increase in the production of endothelium-derived nitric oxide synthetase (eNOS). This, in turn, enhances the production of nitric oxide and supports vasodilation [23]. This increased eNOS expression results in the elevated production of nitric oxide within the endothelium, which supports vasodilation [24][25]. NO release serves not only to facilitate vasodilation but also to hinder leukocyte adhesion, prevent platelet aggregation, and reduce the proliferation of vascular smooth muscle. As a result, NO plays a protective role, and inadequate levels indicate a greater risk of cardiovascular events [26].

A schematic representation in **Figure 1** shows alterations in the vessel wall and endothelial cell membrane that occur during hyperlipidemia. These changes include LDL introduction, monocyte adhesion, platelet aggregation, foam cell formation, and the accumulation of cholesterol crystals in the intima. Alterations in the endothelial cell membrane include the presence of cholesterol-rich domains and increased caveolae, where caveolin plays a key role in regulating eNOS. These modifications are attenuated by HMG-CoA reductase inhibitors, which lower LDL levels and inhibit cholesterol and isoprenoid biosynthesis pathways [25].

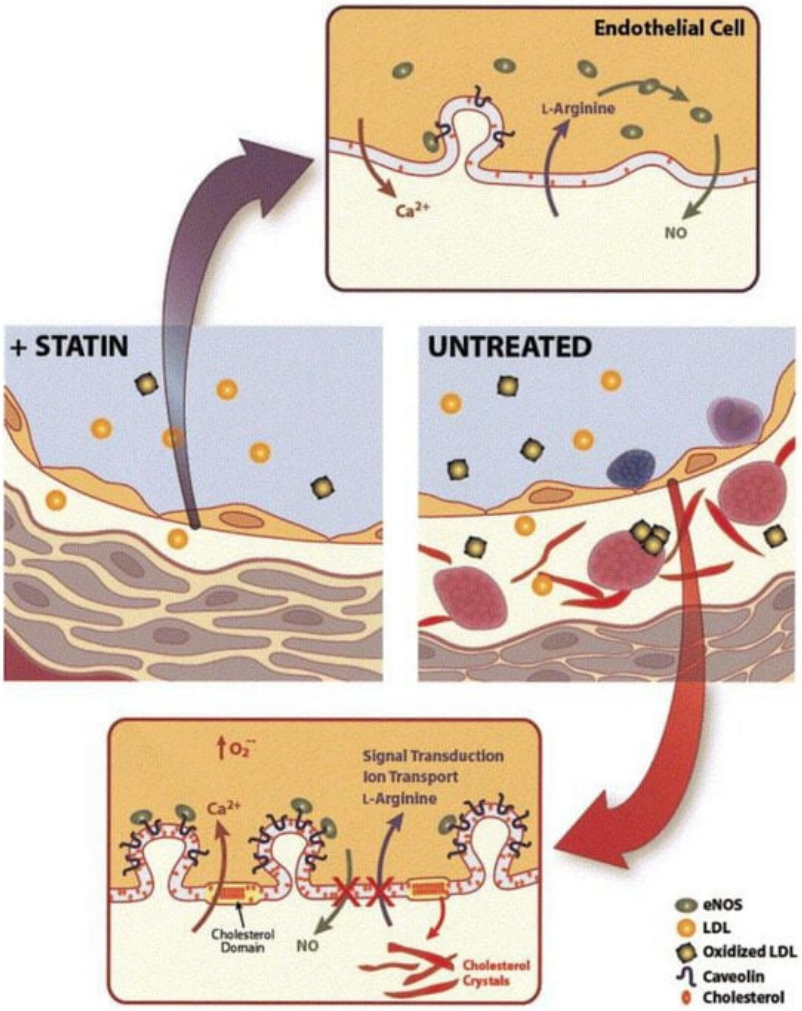

Figure 1. Alteration occurs in the vessel wall and the endothelial cell membrane during the development of atherosclerosis [27].

2.2. Plaque Stabilization

High-intensity statin therapy has been shown in various clinical trials to stabilize and even regress atherosclerotic plaque [28][29][30][31][32][33]. Trials such as REVEAL, ASTEROID, SATURN, and studies using advanced imaging techniques such as optical coherence tomography (OCT), coronary computed tomography angiography, and intravascular ultrasound (IVUS) technology have provided evidence of plaque stabilization and reduced progression in individuals on statin therapy [28]. In trials such as the REVEAL study, individuals receiving high-dose statins such as atorvastatin and rosuvastatin witnessed either a lack of atheroma volume progression or a reversal in atheroma growth within a relatively brief timeframe [29]. In the ASTEROID trial, rosuvastatin significantly reduced atherosclerotic plaque in patients over 24 months [30]. This significant regression in plaque underscores the effectiveness of high-intensity statin therapy in reducing plaque accumulation. Similarly, the SATURN trial provided further evidence supporting the efficacy of high-intensity statin treatment [31]. When comparing two high-intensity statins, rosuvastatin, and atorvastatin, it became apparent that both groups displayed a similar degree of atheroma regression after two years of therapy, indicating the ability of high-intensity statins to stabilize atherosclerotic plaques. Furthermore, advanced imaging methods such as optical coherence tomography (OCT) and coronary computed tomography angiography have yielded valuable information about plaque attributes.

2.3. Anti-Inflammatory Effects

After endothelial damage, atherosclerotic plaques undergo infiltration of inflammatory cells. Statins can mitigate this inflammation by efficiently decreasing the production of inflammatory indicators, including C-reactive protein (CRP), serum amyloid A (SAA), interleukins, and adhesion molecules such as intracellular adhesion molecules (ICAM-I). These markers have all been associated with the initiation and recurrence of cardiovascular events. As illustrated in **Figure 2**, statins possess the ability to suppress NF-κB activity, a crucial transcription regulatory protein involved in inflammatory responses. Furthermore, statins can activate the transcription of the NOS gene, thereby enhancing NO production [25].

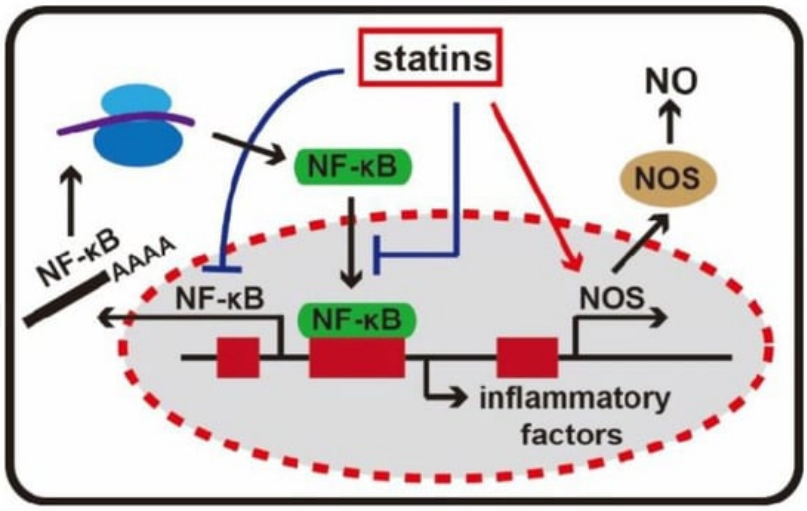

Figure 2. Anti-inflammatory effect of statins [34].

In one of the conducted cohort studies, pravastatin interestingly demonstrates a more substantial reduction in risk among individuals at a high risk of coronary events with elevated SAA and CRP levels compared with those with equivalent cardiovascular risk but normal levels of inflammatory markers [35]. This observation supports the notion that statins do not solely reduce risk by lowering cholesterol but also by suppressing inflammation. Importantly, both atorvastatin and simvastatin can reduce CRP levels, even in patients without elevated cholesterol [36][37], indicating that statins could be beneficial for individuals with normal LDL but heightened inflammatory markers.

2.4. Immunomodulatory Effects

There is informal evidence to suggest that statins may possess anti-inflammatory and immunomodulatory properties, which could be beneficial in conditions such as cardiac transplant rejection and various autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, lupus, vasculitis, and systemic sclerosis [38]. Statins inhibit the induction of MHC-II expression by interferon γ (IFN-γ), leading to the repression of MHC-II-mediated T-cell activation. This effect is due to the inhibition of the inducible promoter IV of the transactivator CIITA and is observed in various cell types. MHC-II molecules play a crucial role in antigen presentation and T-cell activation through the T-cell receptor (TCR). TCR activation can impact T-cell proliferation, differentiation, and cytokine release. Cytokines released by activated T cells stimulate further T-cell proliferation, activate antigen-presenting cells (APCs), and promote B-cell antibody production. CD4+ helper T cells (TH cells) can differentiate into two distinct effector cell populations, TH1 and TH2, each producing different cytokines. Shifting the balance from TH1 to TH2 responses is beneficial in diseases characterized by delayed-type hypersensitivity reactions, such as graft atherosclerosis and chronic inflammatory conditions. Statins can induce this shift from TH1 to TH2 lymphocytes [39][40].

2.5. Anti-Thrombotic Effects

In the final stage of atherosclerosis, damage to the endothelium can lead to the formation of blood clots that obstruct blood flow. Statins can impede the formation of blood clots through multiple mechanisms, including a reduction in tissue factor expression and the inhibition of platelet aggregation [41][42][43]. This results in a decrease in thrombin production and the expression of its receptor on platelet surfaces. In addition to preventing blood clot formation, statins also promote the dissolution of clots by reducing levels of plasminogen activator inhibitor 1 (PA1-1) and enhancing the activity of the fibrinolytic enzyme plasminogen. The anticoagulant properties of statins were demonstrated in the JUPITER study, which showed a decreased rate of peripheral venous thromboembolism in patients taking rosuvastatin [44][45].

2.6. Reduced Oxidative Stress

Many studies suggest that statins have the potential to reduce oxidative stress through various mechanisms, including the inhibition of ROS production, enhancement of antioxidant defenses, protection of endothelial cells, and anti-inflammatory effects [46]. The metabolites of atorvastatin, particularly hydroxy metabolites, exhibit the ability to inhibit the oxidation of LDL, HDL, and VLDL particles. This suggests that statins may exert an antioxidant effect that could contribute to impeding the progression of atherosclerosis independently of their LDL-lowering effects [47]. Statins not only hinder the production of cholesterol but also disrupt the generation of Rac1, a protein involved in activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the production of reactive oxygen species (ROS) [48]. These ROS can contribute to

various negative effects such as endothelial dysfunction, inflammation, and oxidation of LDL particles, all of which play roles in the development of atherosclerosis [49].

2.7. Protection from High-Decibel Noise-Inducing Hearing Loss

In a recent study, researchers evaluated the potential of statins as a treatment for hearing loss in CBA/CaJ mice [50]. They investigated the effects of delivering fluvastatin directly to the cochlea and administering lovastatin orally, assessing hearing outcomes using methods such as auditory brain stem responses (ABRs). Mice were exposed to two hours of octave band noise. Previous research with guinea pigs had demonstrated the protective effects of fluvastatin in the contralateral cochlea. Exposure to high-intensity noise (120 dB SPL for 4 h at 4–8 kHz) was found to result in the loss of hair cells—a phenomenon absent in guinea pigs subjected to noise but treated with fluvastatin. [51].

2.8. Enhance Responses to Immune Checkpoint Blockade in Cancer Models

In the early stages of statin research, concerns arose about a potential link between statin use and cancer risk, particularly with lipophilic statins such as simvastatin [52]. Early observational studies suggested a link between statins and an increased risk of certain cancers [53]. This concern originated from the understanding that statins, acting as cholesterol-lowering agents, influence cellular processes associated with cancer development. The reduction in cholesterol, crucial for cell membrane integrity, raised theoretical concerns about long-term consequences. However, as more robust studies unfolded, these early apprehensions lacked consistent support.

3. Adverse Effects of Statin Therapy

Statin therapy has frequently been associated with several unintended adverse effects, which further contribute to the concept of statin pleiotropy (**Figure 3**).

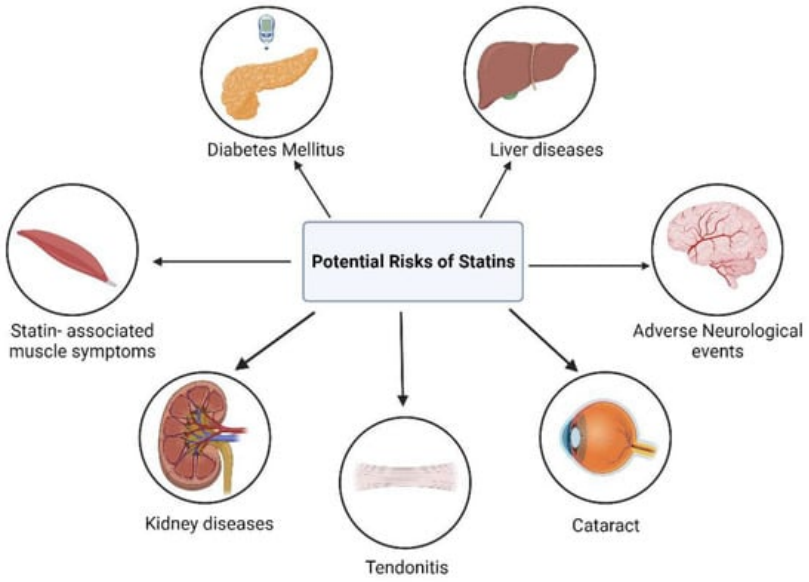

Figure 3. Potential Risks associated with the use of Statins. Created with Biorender.com. Accessed on 6 October 2023.

3.1. Myopathy and Rhabdomyolysis

The most common side effect associated with statin use is muscle-related symptoms. Myopathy is typically characterized by muscle pain, tenderness, or weakness, accompanied by a significant increase in blood creatine kinase (CK) levels, which frequently exceed ten times the upper limit of normal (ULN) in laboratory tests. Creatine kinase is an enzyme released when muscle cells are damaged. Rhabdomyolysis is a severe form of myopathy where CK levels exceed 40 times the ULN. This condition involves the breakdown of muscle tissue, releasing myoglobin into the bloodstream. This can potentially result in sudden kidney failure or impaired renal function. This condition is characterized by significantly higher elevations in creatine kinase levels [54][55]. Preclinical research suggests that statins can reduce mitochondrial activity, lower energy production, and impact muscle protein breakdown, potentially linking statin use to muscle-related symptoms [56]. Clinical and scientific studies have been used to investigate the mechanisms underlying muscular side effects associated with statin therapy [57]. Muscle biopsies of statin-treated patients with normal creatine kinase (CK) levels revealed mitochondrial dysfunction, lipid accumulation, and structural changes.

3.2. Diabetes Mellitus

Data from RCTs show an increased incidence of diabetes mellitus during statin therapy is due to the patients who are already at a higher risk of diabetes progressing to diabetes earlier than they would have otherwise [58][59]. Patients develop chronic insulin resistance and experience a progressive loss of beta-cell function over an extended period of time, leading to the development of type 2 diabetes mellitus [60]. The JUPITER trial observed elevated levels of glycated hemoglobin in individuals taking rosuvastatin, along with a slight increase in the occurrence of diabetes mellitus (3.0% vs. 2.4%, $p = 0.01$) compared with those on placebo [44][61].

3.3. Liver Diseases

The research on the effects of statins on liver disease has demonstrated both potential benefits and concerns. On the positive side, statins have been associated with improvements in liver enzyme levels and a potential reduction in the progression of non-alcoholic fatty liver disease (NAFLD) [62]. On the contrary, initial clinical trials of statins observed increased aminotransferase levels in around 2% of patients. A common side effect, often resolving when the dosage is reduced, is the asymptomatic elevation of hepatic enzyme activity [63]. Despite their widespread use worldwide, acute liver failure has been rare. However, Statin-induced drug-induced liver injury (DILI) causing acute liver failure (ALF) remains a concern [64].

3.4. Adverse Neurological Events

Neurological conditions associated with statin use include hemorrhagic stroke, cognitive decline, peripheral neuropathy, depression, memory issues, aggression, and personality changes [65]. The impact of statins on intracerebral hemorrhages (ICH) has been debated, with some studies suggesting a potential risk increase [66], while recent comprehensive research and meta-analyses did not find a clear association between statin use and ICH [67][68][69].

The impact of statin medication on memory loss has been investigated with varying findings. Some studies suggest that statin use could lower the risk of cognitive decline or dementia, including Alzheimer's disease. These potential neuroprotective effects are hypothesized to be related to statins' anti-inflammatory and antioxidant properties, which may benefit brain health. However, in some studies, no compelling evidence was discovered indicating a connection between statins and Alzheimer's disease or cognitive function [70][71].

3.5. Cataract

Observational data, along with limited preclinical research, suggested a potential link between the use of statins and the development of cataracts. In a clinical investigation, the researchers highlighted that triparanol could trigger cataracts in both white rats and human subjects. As a result of the occurrence of cataracts and other side effects in individuals in various age groups, the therapeutic application of triparanol was discontinued [72].

3.6. Kidney Diseases

According to a study conducted by the Canadian Network for Observational Drug Effect Studies (CNODES), individuals taking high-potency statins, as opposed to low-potency ones, faced a 34% higher risk of being hospitalized for acute kidney injury (AKI) within 120 days of starting treatment [73]. In the first two years of commencing lower-dose statin medication, approximately 1 in 500 patients needed hospitalization for AKI. For those using more potent statins during the same period, there was a 15% higher relative risk of experiencing renal damage [73].

3.7. Tendonitis and Tendon Rupture

According to numerous studies and case reports, statins may increase the risk of tendon rupture [74]. In a case-control study conducted, exposure to statins was compared between 93 cases of tendon rupture and 279 sex- and age-matched controls. There was no significant difference in statin use rates between cases and controls. However, subgroup analysis revealed that statin exposure was a significant risk factor for tendon rupture in women but not in men [75].

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