

Lipid lowering and additional pleiotropic effects of statins.

Lipid düşürücü ve pleiotropik etkileriyle statinler.

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ABSTRACT

Statins are among the most commonly prescribed drugs worldwide today. They are primarily effective in primary and secondary prevention of cardiovascular diseases with their cholesterol-lowering properties. Recent studies have reported that statin derivatives have positive outcomes in different clinical conditions with different mechanisms, in addition to their lipid-lowering effects. In this paper, we aimed to discuss the pleiotropic effects of statins in addition to their protective effects in cardiovascular practice.

Key Words: Pleiotropic effects, statins, antihyperlipidemic

ÖZ

Dünya çapında statinler günümüzde en sık reçetelenen ilaçlar arasında yer almaktadırlar. Temel olarak kardiyovasküler hastalıklardan birincil ve ikincil korunmada kolesterol düşürücü özellikleriyle etki göstermektedirler. Son zamanlarda yapılan çalışmalarda statinler türevi ilaçlarla mevcut olan lipid düşürücü etkilerinin yanında farklı klinik durumlarda farklı mekanizmalarla olumlu sonuçlar elde edildiği bildirilmiştir. Bu yazımızda statinlerin kardiyovasküler hastalıklardaki koruyucu etkileri dışında pleiotropik etkilerinden de bahsetmeyi amaçladık.

Anahtar Kelimeler: Pleiotropik etki, statinler, antihiperlipidemik

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Serum cholesterol levels, particularly LDL cholesterol, are closely related to the development of atherosclerotic cardiovascular disease. Many randomized clinical trials investigating lipid-lowering treatments have found that lowering LDL cholesterol reduces the incidence of atherosclerotic cardiovascular disease. Statins (3-hydroxy-3methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) decrease serum cholesterol levels, primarily LDL cholesterol. The role of statins in primary and secondary prevention of cardiovascular diseases has long been proven in clinical studies. Some of these beneficial effects are independent of LDL cholesterol decrement and have been

described as pleiotropic effects. Pleiotropy associated with statins has been investigated not only in the cardiovascular system but also in non-cardiovascular conditions. Through cellular and molecular mechanisms that have not yet been fully elucidated, statins have shown beneficial effects in renal function, infectious diseases including sepsis, rheumatic diseases, gastrointestinal diseases, neurological disorders, periodontal diseases, bone fractures, and malignancies [1]. In this mini-review, we aimed to summarize the cardiovascular and non-cardiovascular pleiotropic effects of statins, in addition to the cardiac protection they provide through their LDL cholesterol lowering effects.

Statin dosage of patients with a very high risk profile should be adjusted depending on the presence of atherosclerotic heart disease. According to 2021 European Society of Cardiology (ESC) Guidelines about Cardiovascular Disease Prevention, the target LDL cholesterol level should be <55 mg/dL (<1.4 mmol/L) in patients with established atherosclerotic heart disease or in type 2 diabetes mellitus patients with a very high risk profile [2]. Potent statins such as atorvastatin (40-80 mg/day) or rosuvastatin (20-40 mg/day) should be chosen to prevent adverse coronary events in patients with a very high risk. Beside LDL cholesterol lowering effect, potent statins stabilize unstable coronary plaques in acute coronary syndrome patients [3].

Statins reduce the incidence of perioperative cardiac events in high-risk cardiovascular surgery patients. However, there is limited data on the perioperative role of statins in intermediate-risk noncardiac, nonvascular surgery patients. Raju MG et al. reported in their retrospective study involving 752 patients, statin usage was associated with a lower composite endpoint of in-hospital nonfatal myocardial infarctus, new onset atrial fibrillation, and 30-day all-cause mortality [4]. Despite the widespread use of statins in patients undergoing surgery, the results of randomized controlled trials on the effects of starting statins in the perioperative period are not clear. Therefore, routine initiation of statins in the perioperative period is not recommended. However, in patients undergoing high-risk surgery, such as vascular surgery, initiation of statins in the perioperative period is recommended [5].

The blood-brain barrier is the most centrally located point of the neurovascular structure and plays a key role in the maintenance of internal continuity of the central nervous system and the regulation of homeostasis. The role of the blood-brain barrier in the development and progression of ischemic stroke has been demonstrated. Various neuroprotective drugs have been researched to provide neuroprotective effects and improve prognosis in ischemic stroke patients. It has been shown that statins improve neurological functions, reduce inflammation, and increase angiogenic and synaptic connections in ischemic stroke patients. It has also been determined that statins have protective and reparative effects on the blood-brain barrier via components of the neurovascular

unit [6].

Some specific types of cancer that use the mevalonate pathway associated with the HMG-CoA reductase enzyme have been shown to benefit from statin therapy. It has been suggested that these beneficial effects may be independent of cholesterol reduction [7]. In another study involving breast cancer patients, statin use after breast surgery was found to be associated with less metastasis onset, fewer metastatic foci, less death, longer metastasis-free survival, and greater overall survival percentage [8]. In the subgroup analysis according to type of statin used, rosuvastatin, a relatively hydrophilic statin, was observed to have more positive clinical outcomes than the others.

Although current treatment approaches such as immobilization, surgery, and bone grafting are effective in bone fractures, they have disadvantages such as long recovery periods and high costs. The biological agents, pharmacological treatments, and physical stimulation techniques that are being studied have also high costs, possible side effects, and practical difficulties. Low-cost, safe, and easy-to-apply alternative treatment options are needed in this context. Recent studies have reported that statins accelerate bone healing through increase in bone formation and reduction in bone resorption via various biochemical pathways [9]. Another issue concerning bone tissue is the osteonecrosis of femoral head. Patients who use steroid for a long period are particularly at risk for this. Adipogenesis and mitochondrial cardiolipin metabolism disruption can play role in the development of osteonecrosis of the femoral head [10]. In vitro and animal studies have shown that statin use may have a positive effect in preventing the development of osteonecrosis of the femoral head due to steroid use [11]. Prospective, long-term clinical studies are needed to examine this protective effect of statins [12].

We believe that the role of statin derivatives, which have been used in our clinical practice so far due to their lipid lowering effects in primary and secondary prevention of cardiovascular diseases, will increase with further studies on their pleiotropic effects in cardiovascular and non-cardiac conditions.

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