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A mini-review to the common adverse-effects of statins

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Abstract
HMG-CoA (3-hydroxy-3-methyl glutaryl coenzyme A) reductase inhibitors are associated with muscle injury. Chronic kidney disease (CKD) carries a high risk for the development of statin-induced myopathy. Statin therapy decreases the absolute risk of cardiovascular diseases in patients with CKD; however, rhabdomyolysis increases with deteriorating kidney function.
Keywords: Statin, Myopathy, Rhabdomyolysis, HMG-CoA reductase, Apoptosis, Cholesterol-lowering drugs, Low-density lipoprotein cholesterol
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Introduction

The most popular metabolic syndrome is type 2 diabetes, which characterize by defects in quantity and quality of insulin receptors. One of the most common causes of mortality among patients with diabetes are atherosclerosis due to dyslipidemia and hyperglycemia (1). Atherosclerosis as the diabetic macroangiopathy, is supposed as a consequence of chronic inflammation and damage to the arterial intima. After injury to the endothelial cells, a process of micro-inflammation started then oxidized low-density lipoprotein deposits in the endothelial vessel walls (2). Statins as a cholesterol-lowering agents are commonly prescribed for the therapy and prevention of coronary cardiac disease (3), since high low-density lipoprotein cholesterol (LDL-C) and total cholesterol and also high triglyceride are the risk factors for this disease (3). Statins as the analogues of HMG-CoA (3-hydroxy-3-methyl glutaryl coenzyme A), act by inhibition of HMG-CoA reductase (4). Following the stopping of conversion of "3-hydroxy-3-methyl glutaryl coenzyme A" to mevalonate, these drugs diminish cholesterol production in the hepatocytes (5). These drugs are the keystone for prevention of heart and vessels diseases in general population and in diabetics (6). In type 2 diabetic patients, cardiovascular disease is the principal cause of mortality and morbidity (7). However, in clinical practice statins are accompanied by some side effects, which in this mini-review we discuss the myopathy and rhabdomyolysis and apoptosis by these agents.

Search strategy

For this review, we searched Web of Science, EBSCO, Scopus, PubMed/Medline, DOAJ (Directory of Open Access Journals), Embase and Google Scholar using various keywords including: statin, myopathy and rhabdomyolysis, HMG-CoA reductase, apoptosis, cholesterol-lowering drugs, and low-density lipoprotein cholesterol.

Myopathy and rhabdomyolysis

HMG-CoA reductase inhibitors are associated with muscle injury. These might include slight serum creatine phosphokinase elevation, muscle pain, intense myasthenia, painful muscle contractions, muscle swelling, and rhabdomyolysis. Muscle injuries are infrequent, but could be fatal if developed. Myopathy and progression to rhabdomyolysis are dose-dependent and associated with increase statin plasma concentrations. The most serious effect of rhabdomyolysis releases myoglobin from injured muscles, which can lead to acute kidney injury (AKI). While all statins are associated with side effects, such as myopathy, the degree of these adverse effects differs amongst medications within the statin class.

Chronic kidney disease (CKD) carries a high risk for the development of statin-induced myopathy (8). Statin therapy decreases the absolute risk of cardiovascular diseases in patients with CKD; however, rhabdomyolysis increases with deteriorating kidney function (i.e. progressing stages of CKD). Moreover, statin-associated rhabdomyolysis is more common in CKD patients than in the general population (9).

Rhabdomyolysis from statin monotherapy is uncommon. There is a mean of 0.44 cases per 10 000 patients administered statin therapy. Certain concomitant medications may interact with HMG-CoA reductase inhibitors and increase the risk of adverse effects, such as

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Implication for health policy/practice/research/ medical education

Statin-associated rhabdomyolysis is more common in chronic kidney disease patients than in the general population.

myopathy. Since statins are chronic medication therapy, patients can take concomitant medications during this treatment period that interacts with statin therapy. The risk of rhabdomyolysis possibly will be up to 81% in patients administered statin therapy alongside illicit drugs or alcohol. Additionally, statin-induced rhabdomyolysis was observed when fibrates or fusidic acid were concomitantly administered with statin therapy (10). Drug interactions, such as those that worsen rhabdomyolysis, may be due to hydrophobicity or hydrophilicity of interacting medications and the use of the same metabolic pathways as statin therapy.

There are various reports of statin-induced rhabdomyolysis in the literature, either as monotherapy or alongside other medications, for all statins other than fluvastatin (11). In addition to high-dose statins, vitamin D deficiency would also enhance the risk of myotoxicity (12). Vitamin D status can be considered a risk factor for muscle and skeletal-related side effects of statins and administration of vitamin D may help recover statin myotoxicity (13,14).

Three potential mechanisms for statin-induced myopathy have been suggested thus far.

One proposed mechanism suggests that inhibited cholesterol biosynthesis might change myocyte cell membrane permeability. In the presence of cholesterol, lipid membranes naturally increase rigidity and thickness and have lower permeability for small solutes (15). Statins inhibit cholesterol synthesis, which leads to decreased glycosphingolipids receptor numbers and membrane stiffness (16). Then, this leads to changes in the behavior and permeability of myocyte membranes.

Another mechanism proposes that statins inhibit mevalonic acid, a precursor of ubiquinone (coenzyme Q), which is used to promote electron transport in cellular respiration and produce adenosine triphosphate (ATP). Statins reduce ubiquinone levels by 16%-54% and this effect could be further amplified by exercise. Thus, reducing ubiquinone levels likely limits cellular energy production, enzyme activity in the mitochondria, energy transfer in skeletal muscles, and causes subsequent mitochondrial dysfunction and cell death (17).

The final proposed mechanism is that statins inhibit isoprenoid synthesis (a product of the HMG-CoA reductase pathway). Statins might induce a reduction of isoprenoid production and thus inactivate small GTPases, particularly Rab, which are important for statin-induced myopathy (8). It is hypothesized that depletion of isoprenoid production with statin treatment will increase the phosphorylation of tyrosine and activate certain pathways. This process may lead to an increase of cytosolic calcium, the activation of calpain, the activation of some caspases, and finally, apoptosis (18). Previous trials on this subject also demonstrated an increased risk of rhabdomyolysis associated with high doses of simvastatin (19-21).

Apoptosis

The apoptotic effects of statins are suggested to depend upon diminished isoprenylation. The actin-based cytoskeleton is modulated by the Rho sub-family of small G-proteins. Therefore, statins reduce isoprenylation and induce disruption of small G-protein functions and their biological effects, such as cell growth, cell differentiation, and regulation and organization of actin cytoskeleton. This leads to increased P53 protein synthesis and apoptosis (22). Actin disruption could activate DNase, which is known to split DNA and induce apoptosis of proximal tubular cells (23). Several investigations demonstrate that statin-induced apoptosis is potentially prompted by isoprenoid depletion, which results in elevated levels of cytosolic calcium and activation of mitochondrial-mediated apoptotic signaling (18). Simvastatin rapidly induces the tyrosine phosphorylation of cellular proteins in L6 myoblasts and, thus, apoptotic cell death (24). Furthermore, a previous study demonstrated lovastatin to have an apoptotic effect on a certain type of monkey renal cells (25).

Alternatives to statins

A common alternative to statin therapy due to intolerable side effects or ineligibility is ezetimibe (the only cholesterol absorption inhibitor currently available on the market). Ezetimibe could be administered in combination with statin therapy to produce earlier clinical effects and a more pronounced reduction in LDL-c.

Ezetimibe administered with statin therapy rather than high-dose statin therapy is an appropriate alternative for reducing plasma cholesterol concentration in select patients.

Author's contribution

HN is the single author of the manuscript.

Conflicts of interest

The author declares that he has no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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