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Commentary

Statins for Cardiovascular Disease, are they Toxic?

James D Adams*and Eric J Lien

Benicia, CA, USA.

***Corresponding author**
James D Adams, Benicia, CA, USA.

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Abstract

Statins are widely used and are considered safe for almost everyone above the age of 40 or so. Statins are implicated in muscle damage, induction of diabetes, depression and Parkinson's disease. Some of these problems are reversible with statin withdrawal, some are not. The inhibition of protein isoprenylation by statins is important in many of these toxic reactions. The benefits of diet and exercise in these patients cannot be overestimated. Patients should be encouraged to exercise and diet until statins can be withdrawn

Keywords: Statins, Cholesterol, Protein isoprenylation, Diabetes, Muscle toxicity, Depression, Parkinson's disease

Introduction

Cardiovascular disease is the leading cause of death in the US, with 696,962 deaths in 2020 according to the CDC [1]. Blood cholesterol levels are involved in this disease process such that drug therapies to decrease blood cholesterol are prominent in healthcare. Statins are the drugs of choice in hypercholesterolemia, especially high dose statins [2]. The current goal appears to be the prescription of statins to everyone over the age of 40, for the remainder of their lives [3]. For every 1 mmol/L decrease in LDL-cholesterol the risk of major vascular events decreases by about 20% [4].

Peripheral artery disease is another consequence of high blood cholesterol and results in 57,000 deaths and 148,000 amputations annually [5]. Apparently fewer than 20% of these patients take statins [5]. Physicians are being encouraged to prescribe statins in these patients.

Statins are considered to be safe drugs and are effective even in patients above 75 years old [4]. They have a low incidence of side effects and decrease the risk of death from stroke or heart attack by 25% [6]. The use of statins by the general population is currently improving healthcare, saving several billion dollars every year and could save more if people over the age of 40 would comply better with statin therapy [7]. It has been estimated that 40-75% of patients stop taking statins within one year, mostly due to toxicity problems, especially muscle toxicity [8].

Pharmacology

Statins were initially found in red yeast rice, a food and food additive in China. Naturally occurring statins occur in mushrooms and other fungi. Statins are currently used in purified form or as chemical analogs of naturally occurring statins. The 2018 US market for statins was $24.5 billion for over 21 million statin prescriptions sold [9].

Inhibition of hydroxymethylglutaryl CoA reductase (HMG CoA reductase) is the primary target of statins [7]. This enzyme produces mevalonic acid which is necessary for cholesterol synthesis which largely occurs in the liver. Inhibited mevalonic acid synthesis lowers blood cholesterol levels. Lower intracellular levels of cholesterol cause the induction of sterol regulatory element binding protein (SREBP) which increases the synthesis of low density lipoprotein (LDL) receptor [10]. Higher expression of LDL receptor on hepatocyte plasma membranes increases the uptake of LDL cholesterol from the blood, thereby decreasing blood LDL cholesterol levels. Decreased cellular mevalonic acid has other effects, such as decreased protein isoprenylation. This alters the activities of many enzymes.

SREBP induction has many effects including increasing the

synthesis of fats in the cell [10]. Another effect of statins is the induction of peroxisome proliferator activated receptor gamma (PPARγ) which depends on SREBP activation [11]. PPARγ is a nuclear receptor that regulates the transcription of fatty acid storage and glucose metabolism enzymes. Therefore, statins increase intracellular fatty acid synthesis and storage. They can also stimulate glycogen synthesis.

Chemistry

Atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin are currently approved for use in the USA. The chemical structures of these compounds all contain an analog of hydroxymethylglutarate that binds to the active site, a hydrophobic ring system that binds to the reductase enzyme, and side chain functionalities that are important to solubility and enzyme binding.

These drugs can be administered as lactones (Figure 1) that are prodrugs for the active acid forms. The lactones are lipophilic with lop P values of 2.4 to 4.9 [12]. The larger the lop P value, the more lipophilic. Enzymes in the liver cleave the lactones to make acids [13]. It is also possible that enzymes in gut fungi and bacteria cleave the lactones making acids [14]. The acids are much less lipophilic than the lactones, and therefore less likely to penetrate across membranes. Statins penetrate across the blood brain barrier, perhaps due to carrier mediated processes [15].

Pravastatin, atorvastatin, cerivastatin, fluvastatin, pitavastatin and rosuvastatin are administered as acid forms. They may cyclize in stomach acid to form lactones or may be taken up across the gut as acids. Many statins are extensively metabolized in the liver with metabolites appearing in the urine and feces.

Figure 1: Lovastatin lactone is lipophilic (log P=4.27). Lovastatin acid is less lipophilic (log P=1.90).

Effects on Muscle

The FDA released statements in 2016 and 2017 about muscle damage with lovastatin or high dose simvastatin [16, 17]. The use of high dose, 80 mg, simvastatin is banned in new patients due to the increase in muscle damage, including rhabdomyolysis, in the first year of therapy. Lovastatin has several drug interactions that must be considered in order to avoid muscle toxicity [16]. Muscle toxicity is associated with pain, weakness, elevated blood creatine kinase and other symptoms. The two FDA statements clearly indicate that prolonged statin therapy or high blood levels of statins increase the risk of muscle toxicity. One of the consequences of rhabdomyolysis is kidney damage.

Immune mediated necrotizing myopathy is the most extreme form of statin induced muscle toxicity [18]. Anti-10 HMGCR autoantibodies increase the likelihood of developing this disease. Therapy includes discontinuation of statins, immunomodulatory or immunosuppressive therapies, perhaps for the remainder of the patient's life. Fortunately, this is a rare disease.

Intracellular fat droplets or ectopic fat accumulation in muscle, especially ceramide, can be toxic to muscle [19]. Age decreases the ability of muscle to use fatty acids effectively, which leads to ectopic fat induced muscle toxicity and sarcopenia [19]. Ectopic fats in muscle and other sites correlate with cardiovascular disease [20].

Muscle toxicity may also decrease the production of myokines that are essential for health [21]. Brain derived neurotrophic factor is a myokine that appears to stimulate fat oxidation in muscle. Decorin increases muscle mass. Irisin is involved in fat cell regulation. Osteonectin stimulates bone mineralization. Some interleukins, such as IL-6, are myokines and are involved in muscle building and immune health. Decreasing these myokines due to sarcopenia or muscle toxicity degrades health.

Muscle depends on glycogen for energy. Simvastatin inhibits or increases the synthesis of glycogen in human skeletal muscle depending on whether it is the acid or lactone form of simvastatin [22]. Both forms of simvastatin inhibit glycolysis [19]. This decreases the ability of muscle to exercise. It also increases the synthesis of fatty acids from glucose, which leads to fat droplets in muscle cells.

Effects on Insulin Sensitivity

The liver removes 50% of blood insulin. Skeletal muscle removes about 8% of blood insulin [23]. With muscle cell dysfunction or sarcopenia, the ability of muscle to remove blood insulin may decrease leading to higher blood levels of insulin and insulin resistance [22]. Muscle ectopic fat deposits decrease insulin sensitivity [20]. Ceramide accumulation in muscle inhibits insulin receptor activation [24] which is involved in insulin resistance. Adipokines secreted by ectopic fat also contribute to insulin resistance.

Increased blood insulin levels cause heptatic steatosis [25] perhaps leading to nonalcoholic fatty liver disease. Hyperinsulinemia stimulates lipogenesis in liver and other cells [25]. Fatty liver disease can be monitored as increases in plasma levels of liver enzymes. As liver disease develops, the ability of the liver to clear blood insulin may decrease thereby increasing blood insulin levels. Insulin resistance, which occurs in hyperinsulinemia, is also called type 2 diabetes. There is some evidence that treating fatty liver disease patients with statins is beneficial in terms of cardiovascular health [26].

Effects on the Brain

The FDA issued a warning in 2012 that all statins can cause memory loss, forgetfulness, confusion and amnesia [27]. These effects may take a year to become apparent and disappear about 3 weeks after statin cessation. Although the effects appear to be

temporary, they are troublesome for patients. Cognitive changes appear to be worse for simvastatin and atorvastatin compared to other statins [28]. Dementia, and possibly Alzheimer's disease, are not associated with statin intake as reported in a study of 18,846 patients above the age of 65 [29]. A complex interrelation between age, cognitive ability and statin use has been reported in a large study [30].

There is a report, in 500 patients, that statin use has a detrimental effect on Parkinson's disease and long term outcomes [31]. Statins may induce psychiatric behavioral changes in some patients [32]. These symptoms include anxiety, violence, aggressive behavior, depression and suicide. These symptoms subsided when the drug was discontinued.

Cholesterol is an important component of neuronal membranes and is involved in neuronal transmission. Statins, whether lipophilic or hydrophilic, alter brain cholesterol metabolism [33]. Longterm simvastatin decreases hippocampal cholesterol and impairs memory in mice [34].

Serotonin uptake is regulated by lipids such as geranylgeranyl pyrophosphate, through isoprenylation of the serotonin transporter. These lipids are made from mevalonate such that inhibition of mevalonate synthesis by statins decreases geranylgeranyl pyrophosphate levels leading to increased serotonin uptake [35]. Statins also have direct effects on the serotonin transporter increasing serotonin uptake [35]. Selective serotonin reuptake inhibitors are used to treat depression and anxiety by increasing synaptic serotonin levels. This implies that statins, by decreasing synaptic serotonin, may increase depression and anxiety.

Parkin interacting substrate (PARIS) appears to be involved in causing Parkinson's disease [36]. PARIS is inactivated by isoprenylation, decreasing the onset of Parkinon's disease. Statins inhibit isoprenylation and may increase the onset of Parkinson's disease [36].

Effects on Hemolytic Anemia

There are reports of hemolytic anemia induction by statins [37,38]. This appears to be a rare occurrence. The mechanism is not obvious.

Effects on Cataracts

Cataracts may occur more frequently in statin patients [39], resulting in cataract surgery. A study involving 6024 statin patients found the odds of developing cataracts in men and women increased to 1.29. Cataracts are caused by steroids, alcohol, diabetes and other causes. Perhaps statin induced diabetes causes cataracts.

Diet and Exercise

It has been known for many years due to the Framingham studies that diet and exercise decrease blood cholesterol, increase health and longevity [40]. Of course, patients are encouraged to diet and exercise, but the prescription of statins is easier for the healthcare community and patients. Many patients would rather take statins for the rest of their lives than establish life-long diet and exercise programs. Potential toxicity problems with statins are downplayed by the healthcare industry and the FDA.

Exercise decreases LDL cholesterol and increases high density lipoprotein (HDL) cholesterol [41]. The Centers for Disease Control have published that HDL cholesterol decreases the risk of heart disease [42]. Exercise also keeps muscles healthy and maintains myokine secretion. Diet decreases body fat including visceral and ectopic fat deposits that secrete adipokines that are toxic to the body and increase the risk of cardiovascular disease [43]. These adipokines include: tumor necrosis factor α, visfatin, resistin, leptin, C-reactive protein, angiotensinogen and others.

Exercise has many beneficial effects in the brain such as decreasing depression [44], slowing the progression of Parkinson's disease [45], maintaining cognition during aging [46], improving cognition in early Alzheimer's disease [47], decreasing anxiety [48] and slowing the progression of osteoarthritis [49]. Statins do not have these benefits. By encouraging patients to use statins, instead of exercising, the healthcare community is depriving patients of the benefits of exercise. Patients should be taught how to develop and maintain a balanced program of diet, exercise and overall well being [50].

Patients who have lifelong diet and exercise programs may be encouraged to use statins to decrease the risk of heart attack. These patients may be at low risk of heart attack. The toxicity of statins in these patients is likely more important than lowering heart disease risk.

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