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Review

How to balance cardiorenometabolic benefits and risks of statins☆

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ABSTRACT

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are important for preventing adverse cardiovascular events not only in patients with a high risk of vascular disease but also in those with a low risk, by reducing the levels of low-density lipoprotein cholesterol. Statin is associated with deteriorating glucose homeostasis and an increased risk of diabetes mellitus. Moreover, these off-target effects are dose-dependent; it has also been suggested that renal insult can be caused dose-dependently by statin treatment, in contrast to previous studies showing a renoprotective effect. The 2013 American College of Cardiology/American Heart Association guidelines recommend the use of high-intensity statin therapy, and extend its use to more people at risk of vascular diseases. However, a European committee has expressed concerns about the potential side effects of using statins in a large fraction of the population for extended periods. This is true of Asian people, for whom the disease burden from cardiovascular disorders is not as great as among Western ethnic groups. There are still many unanswered questions on how to balance the cardiovascular benefits with the potential renometabolic risks of statins. Therefore, genetic or pharmacogenetic approaches are needed to define who is more vulnerable to developing diabetes mellitus or acute kidney injury. In particular, more information is required regarding the metabolism of statins, and their off-target or unknown actions and overall impact. These different renometabolic effects of statins should help in formulating optimal therapeutic strategies for patients for reducing overall morbidity and mortality and not just those associated with cardiovascular diseases.

Contents

Abbreviation: ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; eNOS, endothelial nitric oxide synthase; GLUT, glucose transporter; GTP, guanosine triphosphate; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme; ALDL, low density lipoprotein; PPAR, peroxisome proliferator-activated receptor; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species.

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1. Introduction

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are most frequently prescribed in clinical practice to treat or prevent cardiovascular disease (CVD) by reducing the circulating levels of low-density lipoprotein (LDL) cholesterol. At present, more than 25 million individuals worldwide take statins [1]. It has been proven in many large-scale clinical trials that statin treatment reduces cardiovascular morbidity and mortality [2–4]. Statins are known to have additional beneficial effects on the cardiovascular system beyond lowering LDL-cholesterol levels [5–8]. Statins reduce the production and/or activity of reactive oxygen species (ROS), effects that have the potential to inhibit the development of atherosclerosis. Statins also have anti-inflammatory and antioxidative properties [5,7–10].

When statin therapy was first introduced, the possibility of several side effects was raised such as an aggravation of liver enzyme activities and damage to muscle tissue [11,12]. It was also reported that very low levels of LDL-cholesterol might be associated with hemorrhagic stroke [13]. An association of statin treatments or low LDL-cholesterol levels with the development of malignancies was raised [14], but other studies have proven that statin treatment is not associated with oncogenesis [15,16] and instead might have cancer-preventive properties [17,18]. A recent study has shown that statin use in patients with cancer is associated with reduced cancer-related mortality [19].

Of note is the fact that statin treatment has now been proven to be associated with deterioration of glucose homeostasis in several clinical studies and meta-analyses [20–28]. Most recently, renal insult caused by statin treatment has been suggested [29]. Moreover, these off-target effects are dose-dependent; it has also been suggested that renal insult can be caused dose-dependently by statin treatment, in contrast to previous studies showing a renoprotective effect.

The 2013 American Heart Association/American College of Cardiology guidelines recommend the use of high-intensity statin therapy, and extend its use to more people at risk of vascular diseases. However, a European committee has expressed concerns about the potential side effects of using statins in a large fraction of the population for extended periods. This is true of Asian people, for whom the disease burden from cardiovascular disorders is not as great as among Western ethnic groups. There are still many unanswered questions on how to balance the cardiovascular benefits with the potential renometabolic risks of statins.

Therefore, genetic or pharmacogenetic approaches are needed to define who is more vulnerable to developing diabetes mellitus or acute kidney injury. In particular, more information is required regarding the metabolism of statins, and their off-target or unknown actions and overall impact. These different renometabolic effects of statins should help in formulating optimal therapeutic strategies for patients for reducing overall morbidity and mortality and not just those associated with CVD. In this review, we discuss how to balance the cardiac, renal, and metabolic benefits and risks of statins when treating or preventing CVD.

2. Possible off-target effects of statin treatment

2.1. Association of statin treatment with insulin resistance

There are conflicting data regarding the effects of some statins on the risk of incident diabetes mellitus [21,23,27]. We first reported that high-dose simvastatin and atorvastatin therapies can have greater adverse effects than low-dose therapies on glucose homeostasis in hypercholesterolemic patients [25,26]. In addition, we observed significantly different metabolic effects of pravastatin versus simvastatin[30] or rosuvastatin[31] with equally lipid-lowering dosages in such patients. Consistent with our observations, a meta-analysis of randomized controlled trials has suggested potential differences between individual statins, with pravastatin showing a trend toward a reduction in metabolic risk, and atorvastatin, rosuvastatin, and simvastatin all demonstrating a significantly increased risk for diabetes mellitus versus placebo treatment [32,33].

Recent analyses have demonstrated an increased incidence of diabetes mellitus caused by statin treatment regardless of statin type [21,27]. Moreover, high doses of statins tend to increase the risk of developing diabetes mellitus [21,23,28]. How statin treatments increase the risk of diabetes mellitus is not clearly understood. Experimental studies have suggested that statins might interfere with insulin secretion in pancreatic beta cells, either by decreasing Ca^{2+}-dependent insulin secretion [34] or by interfering with isoprenylation of guanosine triphosphate (GTP)-binding proteins [35]. Statin inhibition of isoprenoid biosynthesis might lead to lower expression of insulin-signaling proteins in adipocytes and to reduced glucose transporter expression or translocation [36]. Indeed, treatments with lovastatin, atorvastatin, and simvastatin decreased isoprenoid synthesis and downregulated glucose transporter (GLUT)-4 expression, leading to a reduction in insulin sensitivity in *in vitro* and *in vivo* experiments [36–38].

Alternatively, statin therapy—particularly at high doses—might interfere with peripheral insulin signaling. Animals treated with very high doses of statins for 12 days demonstrated statin-induced myopathy, with decreases in the expression levels of both phosphorylated Akt and Foxo1 in skeletal muscle [39]. Atorvastatin treatment attenuated GLUT4 expression, inhibited adipocyte maturation, and accelerated glucose intolerance in an animal model [40]. These results suggest a possible effect of statins on insulin signaling in peripheral tissues.

Adiponectin, an insulin-sensitizing adipocytokine linked to the redox system, might be involved in the association between statins and insulin resistance. Individual statins can have different effects on circulating or expressed levels of adiponectin [37]. Statins that increase adiponectin expression might have beneficial metabolic effects such as improved vascular actions of insulin, decreased inflammation, and reduced endothelin-1 secretion in the endothelium. For example, treatment with pravastatin improves insulin sensitivity by increasing circulating adiponectin levels in humans [30]. In contrast, other statins, particularly at high doses, cause unfavorable effects including reductions in insulin secretion and exacerbation of insulin resistance [36,38]. In one human study, simvastatin or rosuvastatin treatment significantly decreased plasma adiponectin levels and insulin sensitivity, whereas pravastatin treatment significantly increased plasma adiponectin levels and insulin sensitivity at equal lipid-lowering doses [30,31]. Thus, differences in metabolic actions by individual statins might be mediated by adiponectin, which is implicated in ROS production and oxidative stress. Further mechanistic and randomized clinical studies are required to address these different metabolic effects and clinical outcomes of statins.

2.2. Association of statin treatment with acute kidney injury

Traditionally, statins have been believed to have renoprotective properties. Previous studies found that LDL stimulated mesangial proliferation, while oxidized LDL was cytotoxic in tissue culture [41,42]. It was also found that mesangial cells treated with LDL showed increased expression levels and secretion of messenger RNAs for fibronectin and monocyte chemoattractant protein-1 in a dose-dependent fashion [43]. Statin treatments inhibited isoprenylation of Ras and Rho GTPases [35], which might decrease