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Statin Treatment, New-Onset Diabetes, and Other Adverse Effects: A Systematic Review

Casper N. Bang · Peter M. Okin

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Abstract Statin treatment prevents cardiovascular diseases probably beyond their lipid-lowering effect. Increasing evidence suggests that statins might increase the risk of new-onset diabetes; however, diabetes is known to increase the risk of cardiovascular diseases. The majority of the literature suggests an increased risk of new-onset diabetes in patients treated with statins in a number of different settings and that the risk appears greatest among the more potent statins. Furthermore, a dose-response curve has been shown between statin treatment and the development of diabetes. Possible mechanisms include muscle insulin resistance, lower expression of GLUT-4 in adipocytes impairing glucose tolerance and suppression of glucose-induced elevation of intracellular Ca^{2+} level. However, other side effects have been reported such as increased risk of myotoxicity, increased liver enzymes, cataracts, mood disorders, dementias, hemorrhagic stroke and peripheral neuropathy, which should maybe be added to the increased risk of new-onset diabetes, when considering the risk- benefit ratio of statin treatment.

Keywords New-onset diabetes · Statin treatment · Review · Cardiovascular prevention · Adverse effects

Introduction

Statins are effective cholesterol-lowering drugs that reduce the risk of cardiovascular disease events including myocardial infarction, stroke, the need for arterial revascularization and possibly atrial fibrillation [1, 2, 3••]. However, benefits of reducing cardiovascular events could be offset by the potential risk of adverse outcomes from lifelong statin use, such as myopathy, rhabdomyolysis, increasing levels of transaminases and possibly lens opacities [4], dementias [5], peripheral neuropathy [6, 7], and hemorrhagic stroke [8]. In addition, accumulating evidence from clinical trials suggests that statin therapy is associated with an increased risk of new diabetes mellitus (Fig. 1). Because diabetes is known to increase the risk of cardiovascular diseases, the subject has achieved great interest.

This review will present and discuss recently published data on the association of diabetes and statin treatment, including potential causal mechanisms.

Background

Statins are a commonly used group of cholesterol-lowering agents that act by inhibiting the enzyme 3-hydroxy 3-methylglutaryl CoA (HMG CoA) reductase, which catalyzes a rate-limiting step in cholesterol biosynthesis. Because of the additional benefit shown with more intensive statin therapy [9, 10], there has been a trend toward using higher doses of statins. Furthermore, cholesterol-lowering is now recommended for a wide range of people at cardiovascular risk, including those with average and below-average lipid levels [11].

Recent Evidence

A recently published large scale study including 1,235,671 participants observed an 18 % increased risk of new-onset diabetes with statin therapy compared to non-treated subjects [12]. The increased risk of new diabetes has been confirmed in

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C. N. Bang (✉) · P. M. Okin
Department of Medicine, Division of Cardiology, Weill Cornell Medical College, New York, NY, USA
e-mail: casperbang@hotmail.com

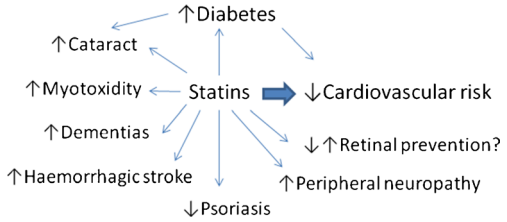

Fig. 1 Wanted and unwanted effects of statin treatment

other large studies and recently published meta-analyses [1, 3••, 13]. In addition, a dose-dependent effect has been demonstrated [3••, 12], further supporting an association of statin use and new-onset diabetes. The Justification for the Use of Statins in Prevention: an Interventional Trial Evaluating Rosuvastatin (JUPITER) study showed that not only was rosuvastatin treatment associated with development of more diabetes, but it was also associated with higher median hemoglobin A1C levels compared to placebo treatment [14]. However, not all studies have found a significant relationship between statin use and new diabetes. Recent data from an observational study including 4740 hypertensive patients without previous diabetes and cardiovascular diseases showed that statins did not increase the risk of new-onset diabetes [15]. Another observational study including 17,080 older patients, aged >65 years, did not find an increased risk of new-onset diabetes with statin use [16]. In contrast, a large observational study from the U.K. using electronic medical records from 500 general practices showed that statin therapy was associated with 14 % increased risk of type 2 diabetes [17]. Analyzing three large randomized controlled trials, Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL), Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) and Treating to New Targets (TNT), Waters et al. [18] demonstrated an increased risk of new-onset diabetes among patients treated with high dose compared with low dose statin treatment. In addition, they found that patients with high fasting glucose levels and components of the metabolic syndrome, specifically higher triglycerides, higher body mass index and hypertension, were significantly more likely to develop new-onset diabetes during statin therapy, as were older as compared to younger patients, when treated with high dose compared to low dose statin therapy [17]. In contrast, a sub-analysis in a larger meta-analysis by Preiss et al. [3••] showed that patients with triglycerides below the median had a higher risk of new-onset diabetes compared to patients above the median when intensive statin treatment was compared to standard statin dose; however, no interaction was found with age, HDL cholesterol level, BMI or fasting glucose level [3••].

A recently published large observational study showed that especially atorvastatin, rosuvastatin, and simvastatin were associated with increased risk of new-onset diabetes compared to pravastatin, while no increased risk was observed for patients treated with lovastatin or fluvastatin. However, when adjusting for dosage, rosuvastatin treatment was no longer associated with development of new-onset diabetes [19]. Atorvastatin but not pitavastatin or pravastatin has showed to increase blood glucose levels [20], which could explain some of the statin type dependent effect.

Possible Mechanisms

Although, association of new-onset diabetes and statin treatment has been demonstrated in observational studies, post-hoc analyses of randomized trials and in large meta-analyses, no clear causal relationship has been found to date [1, 3••, 13].

Given that the degree of increased risk is modest and not completely consistent across studies despite very large cohorts in randomized controlled trials and meta-analyses, it is possible that the association of statin treatment and new-onset diabetes is mediated through other drugs that are commonly given along with statins. A variety of drugs have been shown to increase the risk of diabetes, including beta-blockers [21, 22], thiazide diuretics [21, 22], and glucocorticoids [23]. These are often used together with statin treatment and could in part account for the increased risk of new-onset diabetes in statin users. Patients on statin treatment often suffer from the metabolic syndrome, which is associated with development of new-onset diabetes, and therefore could be another confounder of diabetes development in statin treated patients [18].

The majority of published data, on the other hand, have shown a positive association between statin treatment and new-onset diabetes and a dose response relationship has been reported [1, 3••, 13]. Several studies have examined the relationship of statin treatment to glycemia, plasma insulin levels and insulin resistance. Statin therapy was associated with higher insulin resistance in one study [24]; however, results have been inconsistent [25, 26]. According to data from an animal model, statin induced myopathy was associated with development of muscle insulin resistance [27]. Lipophilic statins, such as atorvastatin and simvastatin, compared to hydrophilic statins, such as pravastatin, have more potent cholesterol lowering effects but are also more likely to result in new-onset diabetes [19], which could be explained by greater effects on skeletal muscle as reflected by their increased association with myalgia [28]. In addition, atorvastatin, but not pravastatin, attenuates expression of GLUT-4 in adipocytes, impairing glucose tolerance [29]. Moreover, simvastatin, but not pravastatin, suppresses glucose-induced elevation of intracellular Ca^{2+} level in a dose related manner [30]. These mechanistic differences between different types of statins could in part explain the varying rates of diabetes onset between statin types. Varying ethnicity or race between studies could also contribute to the differences in recently published data: atorvastatin has been shown to

worsen glycemic control in Japanese [31, 32] but not in European people [33, 34].

Intended and Unintended Effects of Statins

Statin treatment has been shown to reduce the risk of cardiovascular disease events including acute myocardial infarction, strokes, the need for arterial revascularisation and possibly atrial fibrillation [1, 2, 4]. A sudden decrease in statin use was observed in 2009 for all indications which might have been caused by media debate on statin side effects [35]. Therefore it is important to review recent advantages and adverse effects in order to have a solid recommendation and make sure that statins are used appropriately and according to guidelines. The question is whether the beneficial effects of statins could be offset by potential risk of adverse outcomes? In patients without diabetes, Baigent et al. [1] found that lowering LDL-cholesterol by 1 mmol/l prevented five myocardial infarctions for every new case of diabetes that occurred. Supporting this finding, Preiss et al. [3••] pooled data from five large trials (TNT [Treating to New Targets] , IDEAL [Incremental Decrease in End Points Through Aggressive Lipid Lowering], PROVE-IT TIMI [Pravastatin or Atorvastatin Evaluation and Infection Trial], A to Z [Aggrastat to Zocor] and SEARCH [Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine]) comparing high dose with low dose statin treatment and showed that intensive statin treatment increased new-onset diabetes by 12 %; however, in absolute terms, only one case of diabetes occurred for every three cardiovascular cases prevented. In contrast, simple calculations suggest that for every ten patients protected from major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) in JUPITER, seven additional cases of diabetes occurred; and in SPARCL for every ten patients protected from a major cardiovascular event, nine additional cases of diabetes occurred. An important difference between SPARCL and JUPITER and the five trials included in the analysis by Preiss el al. [3••] was that the first two trials compared statin treatment with placebo; and the latter trial compared high dose with low dose statin treatment. One could therefore speculate that intensive statin treatment prevents more cardiovascular risk than increase in new-onset diabetes, which confirms previous studies showing that intensive statin therapy is beneficial [9, 10]. However, Preiss et al. actually demonstrated that intensive statin treatment is more likely to produce new-onset diabetes for every cardiovascular event prevented [3••]. Evidence of increased risk of cardiovascular diseases caused by new-onset diabetes due to statin treatment has not yet been found, which could in part be explained by inadequate duration of follow-up and that the studies were post hoc analyses and not designed to examine this question.

Other Benefits and Adverse Effects

Besides possible increased risk of new-onset diabetes in statin treated patients, other adverse effects have been reported (Fig. 1). Some of the more well known, although rare, are myopathy [4] and rhabdomyolysis that may be caused by statin stimulation of skeletal muscle autophagy based on findings in cultured human rhabdomyosarcoma cells [36]. In addition, statin therapy can be associated with increased levels of liver enzymes that result from changes in the lipid components of the hepatocyte membrane, leading to an increase in its permeability with a subsequent "leakage" of liver enzymes [37]. The possible association of statin use with nuclear lens sclerosis and posterior subcapsular cataract may reflect crystalline lens membrane requirements of high cholesterol levels for proper epithelial cell development and lens transparency [4, 38, 39]; however diabetes is also known to increase these two diseases [39]. Statins also have reported associations with: reduced amyloidogenesis causing dementias [5]; peripheral neuropathy through changes in the membrane composition or function [6, 7]; and hemorrhagic stroke, which may be explained by low levels of cholesterol [8].

In addition to reducing cardiovascular risk, statins therapy may have other beneficial effects. In a study of rat retinas, statin therapy appeared to reduce retinal damage after a transient period of retinal ischemia by modulation of heat shock family of proteins expression in the retina and enhanced retinal ganglion cell survival [40]. However, in a national insurance claims database including 107,007 beneficiaries, among those with elevated lipid levels >1 year of statin use was associated with an increased hazard for exudative age-related macular degeneration [41]. Statins have also been shown to lower PASI-score in psoriasis patients, possibly due to statins anti-inflammatory effect and inhibitory effect on the CCL20/CCR6 interaction that is important in psoriasis development [42].

Conclusions

With the wide-spread use of statin therapy, the adverse effects of statins have become of increasing interest. Although causality is lacking, an increased risk of new-onset diabetes has been demonstrated in a large number of trials. In addition, myotoxicity, increased liver enzymes, cataracts, mood disorders, dementias, and peripheral neuropathy may be associated with statin treatment directly or indirectly through increased risk of diabetes. It seems that patients with high fasting glucose level and components of the metabolic syndrome, specifically higher triglycerides, higher body mass index and hypertension, as well as higher age, are more likely to develop

new-onset diabetes during statin therapy. Although the preventive effects on cardiovascular outcome still outweigh the reported adverse effects, more studies on the later are warranted.

Compliance with Ethics Guidelines

Conflict of Interest Casper N. Bang and Peter M. Okin declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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