Statin use in prediabetic patients: rationale and results to date

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Abstract: Prediabetes increases the risk for new-onset diabetes mellitus in patients receiving statins and this risk is dose- and time- dependent. Explanations for the conversion of a predisposed individual to diabetes are ambiguous including reductions in ubiquinone and adiponectin levels. However, the risk of new-onset diabetes mellitus is far outweighed by the statin-induced considerable decrease in cardiovascular events. Thus, prediabetic patients at high cardiovascular risk should not be denied high-dose statin therapy due to the small increase in the risk of developing diabetes since statins, especially at higher doses, cause greater reductions in cardiovascular events compared with standard statin doses. Moreover, lifestyle modification or even antidiabetic drugs are highly recommended in these individuals.

Keywords: cardiovascular risk, new-onset diabetes mellitus, prediabetes, statin

Introduction

Diabetes mellitus is a worldwide health problem with epidemic proportions which can lead to functional disability, vascular complications and premature death, emphasizing the paramount importance for the prevention or delay of diabetes development [Stratton *et al.* 2000; Liberopoulos *et al.* 2006]. A diabetogenic role for statins has been suggested both from large randomized trials and meta-analyses [Kostapanos *et al.* 2010; Sattar *et al.* 2010; Navarese *et al.* 2013]. Indeed, several statins have been shown to increase insulin resistance indices, glucose levels and glycosylated hemoglobin (HbA1c) [Kostapanos *et al.* 2009, 2010; Anagnostis *et al.* 2011; Florentin *et al.* 2013; Kei *et al.* 2013; Shen *et al.* 2013; Zhou *et al.* 2013]. Statins, however, effectively reduce atherosclerotic complications, irrespective of the gender and the level of glucose metabolism disturbance [Cholesterol Treatment Trialists *et al.* 2008, 2010; Cholesterol Treatment Trialists, 2015]. The risk of statin-associated new-onset diabetes mellitus (NODM) is dose dependent and is increased in patients with pretreatment fasting plasma glucose above 100 mg/dl (prediabetic state), features of the metabolic syndrome, women and older patients [Sattar *et al.* 2010; Preiss *et al.* 2011; Waters *et al.* 2011; Aiman *et al.* 2014]. Previous analyses indicated that the risk of NODM was significantly outweighed by the reduction in

vascular events or deaths among subjects with cardiovascular disease or even high risk patients [Ridker *et al.* 2012; Waters *et al.* 2013]. However, it is not clear if the risk of NODM is also significantly outweighed by the reduction in vascular events in the prediabetic population.

Published data

In an analysis of the Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), participants were stratified on the basis of having none or at least one of four NODM major risk factors: metabolic syndrome, body mass index ≥ 30 kg/m², fasting plasma glucose >100 mg/dl or elevated HbA1c levels [Ridker *et al.* 2012]. In patients with one or more diabetes risk factors, an 28% increase in rosuvastatin-associated NODM was noted, while no increase in diabetes mellitus was noted in those without a diabetes risk factor. However, rosuvastatin decreased cardiovascular events and death by 39% and 52% in low and high risk patients, respectively [Ridker *et al.* 2012]. Specifically, for patients with diabetes risk factors, a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed [Ridker *et al.* 2012]. Furthermore, in an analysis limited to the 486 patients who developed diabetes mellitus during follow up, the point estimate of cardiovascular

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risk reduction associated with statin therapy was consistent with that for the trial as a whole [Ridker *et al.* 2012]. Overall, rosuvastatin administration accelerated the average time to diagnosis of diabetes by 5.4 weeks compared with placebo [Ridker *et al.* 2012].

In a retrospective study including 9035 prediabetic patients, the occurrence of NODM and cardiovascular disease and death was 23.5% and 16.7%, respectively, in statin-naïve subjects and 28.5% and 12.0%, respectively, in statin users during a follow up of 2.5–4.1 years [Wang *et al.* 2014]. Of note, both the increase in NODM and the reduction in cardiovascular disease and death were dose- and time- dependent of the statin treatment [Wang *et al.* 2014].

In a meta-analysis including three trials [Treating to New Targets (TNT) trial, Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial and Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial], baseline fasting glucose was the strongest predictor of atorvastatin-induced NODM [Waters *et al.* 2011]. Higher baseline fasting glucose (≥ 95 mg/dl (5.3 mmol/l)) in each trial was associated with higher NODM risk [Waters *et al.* 2011]. Overall, the conversion rate to NODM generally exceeded 10% over nearly 5 years among atorvastatin-treated subjects with fasting glucose > 100 mg/dl [Waters *et al.* 2011].

In a meta-analysis of the TNT and IDEAL trials, high dose of atorvastatin (80 mg/day) did not increase the incidence of NODM in patients with 0–1 risk factors (fasting plasma glucose > 100 mg/dl, fasting triglycerides > 150 mg/dl, body mass index > 30 kg/m² and hypertension), but did increase by 24% for patients with 2–4 risk factors [Waters *et al.* 2013]. As expected, the administration of lower statin doses (atorvastatin 10 mg and simvastatin 20–40 mg) was associated with decreased NODM incidence in patients with 2–4 risk factors compared with atorvastatin 80 mg [Waters *et al.* 2013]. Compared with low statin doses, however, atorvastatin 80 mg reduced cardiovascular events in patients at both low and high risk for diabetes [Waters *et al.* 2013]. Numerically, among 6231 patients in the IDEAL and TNT trials at high risk for NODM, treatment with atorvastatin 80 mg compared with a lower statin dose was associated with 80 more cases of NODM and the prevention of 94 major cardiovascular events in 58 patients [Waters *et al.* 2013].

Discussion

The mechanisms of statin-induced NODM are not thoroughly understood. Atorvastatin, simvastatin, lovastatin, fluvastatin and pitavastatin are relatively lipophilic compounds, whereas pravastatin and rosuvastatin are relatively hydrophilic [Schachter, 2005]. It has been hypothesized that lipophilic statins might be more diabetogenic as they can penetrate more easily extrahepatic cell membranes such as β cells, adipocytes and skeletal muscles, while hydrophilic statins (e.g. pravastatin) are more hepatocyte specific and less likely to enter β cells or adipocytes [Schachter, 2005]. This hypothesis is also supported by a recent meta-analysis in which pravastatin, in contrast to simvastatin, was found to improve insulin sensitivity [Baker *et al.* 2010]. However, this hypothesis cannot explain the risk of NODM with rosuvastatin (as in JUPITER) [Ridker *et al.* 2012]. In this context a more recent meta-analysis failed to find any difference between lipophilic and hydrophilic statins [Sattar *et al.* 2010]. In a number of trials, statins have been shown to impair glucose uptake by cells involved in the regulation of glucose metabolism (adipocytes, skeletal myocytes) by inducing cholesterol-dependent conformational changes in glucose transporters (GLUT) proteins [Nowis *et al.* 2014]. Cholesterol is required for the condensation of membrane lipids; it rigidifies fluid plasma membrane to reduce passive permeability and increases its mechanical properties and total thickness. Thus, the statin-induced cholesterol depletion disturbs the structure of membrane embedded proteins, including GLUTs [Nowis *et al.* 2014]. Furthermore, inhibition of isoprenoid biosynthesis by statins has been implicated in downregulation of GLUT4 synthesis in adipocytes [Nakata *et al.* 2006; Ganesan and Ito, 2013].

Another mechanism reported from cellular studies showed that statins may also interfere with β -cell insulin secretion either by decreasing calcium-dependent insulin secretion or by interfering with isoprenylation of guanosine triphosphate (GTP) binding proteins [Goldfine, 2012]. In addition, statins are known to cause mitochondrial dysfunction in skeletal muscles that limits their glucose uptake, whereas statin-induced myalgia and fatigue may impair exercise capacity and aggravate sarcopenia, which is associated with glucose intolerance and type 2 diabetes [Srikanthan *et al.* 2010; Sirvent *et al.* 2012].

The latest evidence suggests that statins decrease ubiquinone (CoQ10) levels, especially at higher

doses. Interestingly, by decreasing the pancreatic β -cell adenosine triphosphate (ATP) levels, ubiquinone deficiency delays insulin release [Mabuchi *et al.* 2005]. It has also been proposed that decreased β -cell levels of ubiquinone decrease the mitochondrial glycerol-3-phosphate-dehydrogenase (G3PD) levels, which are critical to the mitochondrial function [McCarty, 1999]. Therefore, correction of ubiquinone levels by supplementation with coenzyme Q10 may help to improve β -cell mitochondrial function, increase β -cell ATP levels and improve glucose-stimulated insulin secretion [McCarty, 1999].

Simvastatin and atorvastatin have been shown to reduce adiponectin levels even though the results are controversial, whereas pravastatin and pitavastatin have been associated with increased adiponectin levels and improved glucose metabolism [Arnaboldi and Corsini, 2015; Chan *et al.* 2015]. Adiponectin is a hormone secreted by adipocytes, which lowers insulin resistance. It suppresses fatty acid induced β -cell apoptosis, which is the most likely mechanism by which β -cell function is decreased in type 2 diabetes, an action mediated through the adiponectin receptors on the pancreatic β -cells [Arnaboldi and Corsini, 2015; Chan *et al.* 2015]. Therefore the consistent and significant increases in adiponectin levels that occur with pravastatin and mainly pitavastatin might explain why only these particular statins may improve glycemic control [Arnaboldi and Corsini, 2015; Chan *et al.* 2015].

Finally, very recent genetic data imply that statin-induced NODM is a consequence of inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the intended drug target [Swerdlow *et al.* 2014]. In this study, the single nucleotide polymorphisms (SNPs) in the *HMGCR* gene, rs17238484 (for the main analysis) and rs12916 (for a subsidiary analysis) as proxies for HMGCR inhibition by statins were studied in 223,463 individuals from 43 genetic studies [Swerdlow *et al.* 2014]. It was found that each additional rs17238484-G allele was associated with a mean 0.06 mmol/l lower low-density lipoprotein (LDL) cholesterol and higher bodyweight (0.30 kg), waist circumference (0.32 cm), plasma insulin concentration (1.62%) and plasma glucose concentration (0.23%), while the rs12916 SNP had similar effects on LDL cholesterol, bodyweight and waist circumference [Swerdlow *et al.* 2014]. Overall, there was a slightly higher risk of type 2 diabetes for the rs17238484-G allele [odds ratio

(OR) per allele 1.02, 95% confidence interval (CI) 1.00–1.05] and the rs12916-T allele (OR 1.06, 95%CI 1.03–1.09) [Swerdlow *et al.* 2014]. Of note, NODM is significantly lower in patients with familial hypercholesterolemia compared with their unaffected relatives [Athiros *et al.* 2014]. These findings may be partly due to the fact that these patients are more willing to follow lifestyle measures and have a low body mass index, thus reducing the risk of NODM [Athiros *et al.* 2014]. In addition, patients with familial hypercholesterolemia may lack activation of sterol regulatory element binding proteins (SREBPs), a fundamental step in the mechanism of LDL receptors' increase [Athiros *et al.* 2014]. In fact, statins increase LDL receptors' expression through SREBP activation, which is causally related to insulin resistance [Liu *et al.* 2012]. If true, this may explain why more potent statins are associated with increased NODM incidence.

It should be mentioned that there has never been a prospective randomized study designed to assess the effect of statins on the risk of developing diabetes. All of the studies discussed in this article are observational and meta-analyses, and as such the results should be interpreted as possible explanations rather than proof of causation. These trials do not indicate an increased risk of diabetes-related complications such as nephropathy, neuropathy and retinopathy with statin therapy. Although the clinical significance of statin-induced diabetes is uncertain, a patient who develops NODM requires glycemic profile monitoring, dietary restrictions and chronic antidiabetic therapy.

When considering the balance between NODM and cardiovascular event prevention, it is noteworthy that both microvascular and macrovascular diabetes complications are not common during the first years from diagnosis, while many patients with established vascular disease will die from an atherosclerotic event before they develop any diabetes-associated complications. Even if the risk for development of statin-induced NODM was the same as the risk of an atherothrombotic event, NODM would be by no means equal to a major cardiovascular event. Furthermore, statins have been associated with reduced microvascular complications in diabetes patients [Nielsen and Nordestgaard, 2014]. Current guidelines recommend that in all patients with high cardiovascular risk considered for statins a risk score (e.g. FINDRISK) for NODM should be initially

applied [Sattar *et al.* 2014]. If their risk score shows low- to moderate diabetes mellitus risk then HbA1c and/or fasting plasma glucose need not to be assessed. In contrast, in patients with both high cardiovascular and NODM risk HbA1c and/or fasting plasma glucose should be measured pre statin and re-assessed 3 months after statin initiation [Sattar *et al.* 2014]. In addition, in patients with a high NODM risk score or prediabetes (fasting plasma glucose above 100mg/dl or HbA1c: 6.0–6.4%), intensive lifestyle changes targeting weight loss or even antidiabetic treatment are recommended [Sattar *et al.* 2014].

Conclusion

Overall, although statins slightly increase the risk for NODM, no change is recommended to current practice because the benefits of statin therapy for the reduction of cardiovascular events in patients at risk for diabetes (including prediabetic patients) outweigh this risk [American Diabetes Association, 2014; Bays *et al.* 2014; Katsiki *et al.* 2014; Maki *et al.* 2014]. However, prediabetic patients should be counseled regarding lifestyle modification, particularly weight loss if overweight or obese, and engaging in adequate physical activity [American Diabetes Association, 2014; Maki *et al.* 2014]. Clinical trials suggest that lifestyle modifications are efficacious in delaying or even preventing NODM in prediabetic patients [Knowler *et al.* 2002; Tabak *et al.* 2012]. The Statin Diabetes Safety Task Force endorses the American Diabetes Association's Standards of Medical Care in Diabetes recommendation that, if applicable, patients with prediabetes receive a referral to an effective ongoing support program targeting weight loss of 7% of bodyweight and at least 150 minutes per week of moderate intensity physical activity, such as walking [American Diabetes Association, 2014; Maki *et al.* 2014]. Last, in very high risk prediabetic patients, antidiabetic treatment, mainly metformin, may also be considered [Sattar *et al.* 2014].

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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