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Could changes in adiponectin drive the effect of statins on the risk of new-onset diabetes? The case of pitavastatin

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Abstract

Statins represent the elective lipid-lowering strategy in hyperlipidemic and high cardiovascular-risk patients. Despite excellent safety and tolerability, reversible muscle-related and dose-dependent adverse events may decrease a patient's compliance. Large meta-analyses, post-hoc and genetic studies showed that statins might increase the risk of new-onset diabetes (NOD), particularly in insulin-resistant, obese, old patients. Race, gender, concomitant medication, dose and treatment duration may also contribute to this effect. Based on this evidence, to warn against the possibility of statin-induced NOD or worsening glycemic control in patients with already established diabetes, FDA and EMA changed the labels of all the available statins in the USA and Europe. Recent meta-analyses and retrospective studies demonstrated that statins' diabetogenicity is a dose-related class effect, but the mechanism(s) is not understood. Among statins, only pravastatin and pitavastatin do not deteriorate glycemic parameters in patients with and without type 2 diabetes mellitus. Interestingly, available data, obtained in small-scale, retrospective or single-center clinical studies, document that pitavastatin, while ameliorating lipid profile, seems protective against NOD. Beyond differences in pharmacokinetics between pitavastatin and the other statins (higher oral bioavailability, lower hepatic uptake), its consistent increases in plasma adiponectin documented in clinical studies may be causally connected with its effect on glucose metabolism. Adiponectin is a protein with antiatherosclerotic, anti-inflammatory and antidiabetogenic properties exerted on liver, skeletal muscle, adipose tissue and pancreatic beta cells. Further studies are required to confirm this unique property of pitavastatin and to understand the mechanism(s) leading to this effect.
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1. Statins and type 2 diabetes mellitus: the state of the art

Several randomized-controlled trials have demonstrated the benefits of lowering low-density-lipoprotein cholesterol (LDL-C) with statins to reduce cardiovascular (CV) risk in a wide range of populations, including patients with type 2 diabetes mellitus (T2DM) [1–3]. Although statins are safe, recent studies highlighted the possibility that they may cause the development of new-onset diabetes (NOD) [4–6]; however, this small risk varies with the baseline risk of developing T2DM [6].

While atorvastatin, simvastatin, rosuvastatin, lovastatin and fluvastatin generally deteriorate glycemic parameters in patients with and without T2DM, pravastatin and pitavastatin seem neutral [6]. The earliest evidence on these differences comes from a post-hoc data analysis from the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction (PROVE-IT) 22 trial, where 3,382 patients without T2DM showed 0.30% and 0.12% increase from baseline in glycated hemoglobin (HbA1c) with atorvastatin 80 mg and pravastatin 40 mg, respectively [7]. To investigate statin-induced risk of developing T2DM, Sattar et al. [5] performed a meta-analysis of 13 trials including 91,140 patients without T2DM. Overall, standard-dose statin was associated with a 9% increased risk for T2DM over 4 years, with little heterogeneity between trials. To corroborate this evidence, later, a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial (N = 3,803) showed that NOD developed in 166 of 1,905 patients randomized to atorvastatin 80 mg/day and in 115 of 1,898 subjects of the placebo group (8.71% vs. 6.06%) [8]. The Canadian Network for Observational Drug Effect Studies Investigators [9] study and a meta-analysis performed by Preiss et al. [4] on data from five trials in which 32,752 participants without baseline T2DM received intensive- versus standard-dose statin, documented that among statins, those with

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higher potency are more likely to increase the risk of NOD. Moreover, these effects seem to be dose-related [4]. NOD, which is more evident in patients with pre-existing T2DM risk factors [8], elderly [5], women [10] and Asians [11,12], is a cause for concern because long-term T2DM is associated with a 2-fold increased CV risk [13,14]. Based on this evidence, FDA changed the labels of all the available statins (pravastatin and pitavastatin included) and of statin-containing combinations in the USA, including warnings about the possibility of increased glycemia and HbA1c, while EMA included the warning in the product information of all the statins authorised in the European Union and issued guidance on an increased T2DM risk.

2. Is statin-induced risk of NOD a class effect?

Retrospective studies and a recent meta-analysis conducted on 246,955 patients from 135 randomized-controlled trials confirmed that statins increase T2DM risk, but no statistical difference was seen among drugs and doses [12,15]. A population-based cohort study performed in 471,250 Canadians without T2DM showed that patients taking atorvastatin, simvastatin or rosuvastatin had an increased risk of developing T2DM versus pravastatin, fluvastatin and lovastatin-treated patients and the order of diabetogenicity was the same, regardless which statin was used for primary or secondary prevention. Although similar results were observed when grouping statins by potency, the risk of incident T2DM associated with rosuvastatin became non-significant when the dose was taken into account [16]. Nevertheless, all these results require confirmation in large-scale, head-to-head clinical trials, since most of these studies did not systematically assess T2DM incidence, were underpowered to detect differences between statins, and were retrospective [6].

Very recently, utilizing data from 20 randomized-controlled trials, Swerdlow et al. [17] not only further documented the increased risk (odds ratio 1.12) of statin-induced NOD, but also tried to understand the mechanism(s) of this effect, using a genetic approach. When they studied single-nucleotide polymorphisms (SNPs) near the gene encoding for the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, previously demonstrated to be associated with changes in LDL-C and evaluated their relationship with waist circumference, body weight, body mass index (BMI), insulinemia, glycemia and risk of T2DM, a slight but significant increased risk of T2DM emerged. Interestingly, since this effect is associated with an on-target reduction in HMG-CoA activity, it implies that the risk of NOD cannot be modified or avoided by new and more specific statins [17]. Moreover, the documented association with BMI may suggest a mechanism downstream of HMG-CoA reductase inhibition, by which increased body weight may increase insulin resistance and diabetes. In fact, among the several hypotheses raised, increases in caloric and fat intake during statin treatment have been related to the onset of NOD [18]. Nevertheless, it has to be underlined that the magnitude of the effect on caloric intake and BMI seems insufficient to account for the increased risk of T2DM; moreover, this effect is not dose-related, differently from statin-induced NOD [17,19]. A recent interesting study demonstrated that the prevalence of NOD is significantly lower in patients affected by familial hypercholesterolemia (n = 14,296) vs their unaffected relatives (n = 24,684) (odds ratio 0.35 and 0.51 respectively for LDL-receptor-negative and LDL-receptor-defective mutations) [20]. Two major explanations have been proposed. The first, always connected to calories retention, suggests that these patients are more willing to follow lifestyle measures, thus contributing to decrease the risk of NOD. The second relies on the fact that these patients may experience a possible lack in activation of Sterol Regulatory Element Binding Proteins (SREBPs), a fundamental step in the mechanism of LDL-receptor increase [18]. In fact, statins increase LDL-receptor expression through activation of SREBP-1a, -1c and -2, which are also causally related to insulin resistance [21]. If true, this may explain why the more potent is the statin, the greater are the possible increase in SREBPs and LDL receptors, as well as reduction in plasma LDL-C and a higher incidence of NOD.

3. Mechanism of NOD: the role of adiponectin

To understand the mechanism(s) underlying statin-induced NOD, several hypotheses have been raised [22–25]. Differences in lipophilicity, effects on calcium channels in β-cells, translocation of GLUT-4 transporter, decreases in ubiquinones, isoprenoids, dolichols, intracellular insulin signal transduction pathways, inhibition of adipocyte differentiation, adiponectin production/secretion and altered lipoprotein metabolism are the most frequently debated, but none of these has been fully convincing. The effects of statins on glucose in experimental models have been extensively reviewed by Koh et al. [26] and, more recently, by Brault et al. [23]. Many of these hypotheses rely on effects that have been demonstrated in *in-vitro* or *in-vivo* experiments, under conditions and at concentrations too far away from the clinical setting, with the result that several of them have not been confirmed in humans.

An interesting, very recent hypothesis has been raised by Henriksbo et al. [27]. Fluvastatin, simvastatin, lovastatin and atorvastatin dose-dependently increase the secretion of the proinflammatory cytokine interleukin-1b (IL-1b) in macrophages, an event that requires caspase-1 activity and priming with an immunogenic agent (e.g. LPS). This phenomenon indicates the activation of the inflammasome containing the pattern recognition receptors (PRR), NOD-like receptor family, pyrin domain containing 3 (NLRP3)/caspase-1, which have been demonstrated to correlate with the development of insulin resistance in rodents [28]. In obese mice, the impaired insulin-stimulated glucose uptake in adipose tissue by long-term fluvastatin treatment is

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