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Editorial

New-Onset Diabetes and Statins: Throw the Bath Water Out, But, Please, Keep the Baby!

In this issue of *Metabolism*, Cho et al [1] evaluated the potential diabetogenic effects of statins. Patients (n = 3680) from a single center in Korea, without impaired fasting glucose or diabetes mellitus (DM), initiated on statin therapy, were retrospectively studied for 63 ± 15 months. There were 208 (5.7%) patients in the pravastatin group (mean dose 23.4 ±7.5 mg/day), 326 (8.9%) patients in the simvastatin group (mean dose 22.9 ± 7.5 mg/day), 628 (17.1%) patients in the pitavastatin group (mean dose 2.0 ± 0.9 mg/day), 1191 (32.4%) patients in the rosuvastatin group (mean dose 11.3 ± 3.4 mg/day) and 1327 (36.1%) patients in the atorvastatin group (mean dose 13.8 ± 8.4 mg/day). Patients who switched to another statin were excluded. There were small baseline differences between groups in terms of gender, age and fasting glucose; body mass index (BMI) was similar between groups.

At the end of the study, 217 patients (5.9%) developed new-onset diabetes (NOD). The incidence of NOD was significantly higher in the pitavastatin group (7.8%) compared with the other groups (6.5, 5.8, 5.1 and 3.4% for rosuvastatin, pravastatin, atorvastatin and simvastatin groups, respectively; p = 0.041) [1]. In multivariate analysis using the simvastatin group as reference, the only significant difference was that the pitavastatin group showed a significantly higher risk for NOD [hazard ratio (HR) 2.68, 95% confidence intervals (CI) 1.26–5.71; p = 0.011]. The other statin groups showed a non-significant trend toward a higher risk for NOD compared with simvastatin. Fasting glucose levels and BMI at baseline were associated with NOD incidence [HR 1.11, 95% CI 1.07–1.14; p < 0.001 and 1.02, 95% CI 1.01–1.04; p = 0.005, respectively]. Patients with NOD took significantly higher statin doses than those not developing NOD only in the atorvastatin group (16.7 ± 13.8 vs 13.7 ± 8.0 mg/day; p = 0.004). Patients taking pitavastatin for primary prevention had a significantly higher incidence of NOD compared with those taking simvastatin (HR = 3.11, 95% CI 1.18–8.19; p = 0.022); however this analysis was based on a small number of patients (49 NOD cases of which 23 had established vascular disease) [1].

We should keep in mind that this study has limitations (e.g. small n, retrospective design and need to adjust for pairwise multiple comparisons), as discussed by the authors [1]. Furthermore, the authors did not report metabolic syndrome (MetS) prevalence and weight changes throughout the study; these variables may influence NOD incidence. Finally, uncontrolled confounding remains a possibility. Previous retrospective studies on statin-related NOD also have limitations, including: power to demonstrate differences between statins, varying dose or duration of statin treatment, baseline DM risk factors, influence of other drugs (e.g. glucocorticoids, thiazides and beta-blockers) and how insulin sensitivity was assessed.

Statin-related NOD is an important issue since statins are widely prescribed to decrease cardiovascular disease (CVD) risk. Previous studies and meta-analyses have reported that patients receiving higher potency statins (atorvastatin and rosuvastatin) may be more likely to develop NOD compared with those using lower potency statins (simvastatin, pravastatin, lovastatin and fluvastatin) [2–4]. However, it should be noted that when analyzed separately, some statin trials [e.g. PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22), A to Z (Aggrastat to Zocor), IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering) and SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) trials] report a trend toward a higher risk for NOD in patients on higher potency statins compared with those on lower potency statins as well as in patients on higher statin doses vs those on lower doses, but these differences do not always achieve significance, whereas pooled data point toward a significantly increased risk for NOD on the basis of statin type and dose [4]. Whether this finding is true remains to be confirmed by well-designed studies given that meta-analyses are potentially limited by shortcomings of the individual studies included.

It has also been reported that statin-related increased risk for NOD was more evident in the first 4 months of treatment with high-intensity statins [5]. In contrast, data on 15,637 elderly hypertensive and dyslipidemic patients showed that patients on atorvastatin and rosuvastatin had a significantly lower risk for NOD compared with those not on a statin, whereas lovastatin and simvastatin had a higher risk compared with non-users independently of age, gender, mean dose and co-administered medications; pravastatin and fluvastatin did not affect NOD incidence [6]. Again, these studies were not prospectively designed to assess subgroups.

It has also been proposed that lipophilic statins passively diffuse into the cells, thus possibly affecting insulin secretion to a greater extent than hydrophilic statins (pravastatin, rosuvastatin) which require a carrier to be transported

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intracellularly [7]. However, rosuvastatin was shown to exert diabetogenic effects despite its hydrophilic properties, possibly due to its higher potency, affinity and, consequently, distribution into cells compared with pravastatin [8]. Therefore, any diabetogenic effect of statins is probably influenced by several factors.

Apart from statin type, it has also been proposed that the greater the duration and/or dose of statin treatment, the higher the risk of NOD [9]. A recent cohort study also reported that NOD risk increased as adherence to statin therapy improved [10]. Furthermore, age, gender and baseline BMI, glucose, total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels as well as LDL-C target levels and relative LDL-C reduction have been associated with statin-related NOD in large randomized clinical trials or meta-analyses [11–13], although there are conflicting results [13].Other risk factors for NOD include Asian ethnicity, family history of type 2 DM and MetS features (e.g. hypertriglyceridemia, impaired fasting glucose, obesity and hypertension) [14,15]. Also, weight gain has been associated with NOD incidence in a recent analysis of the Treating to New Targets (TNT) study [16]. However, in patients with heterozygous familial hypercholesterolemia and familial combined hyperlipidemia, neither long duration nor high intensity statin treatment affected NOD development [17]. The heterogeneity of statin trials with respect to several parameters (e.g. patient characteristics, statin dose, duration of treatment and DM risk factors) may partly explain the different results in relation to NOD as does the fact that all these studies were not primarily designed to study these outcomes.

The molecular mechanisms that may be involved in statin-related NOD include effects on the regulatory pathways of insulin signaling, negatively affecting insulin sensitivity and secretion, pancreatic beta-cell function and adipokine secretion [7,18] as well as single nucleotide polymorphisms in the 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) gene [13,19]. Different effects of statins on glucose uptake via the glucose transporter-4 (GLUT4) pathway in adipocytes have also been reported [20]. It should be noted that these mechanisms, mainly raised by in vitro or animal studies, have not been investigated in depth in humans. The fact that so many mechanisms have been proposed could be interpreted as indicative of doubts regarding the mechanism(s) involved in any causal association between statins and NOD.

Specific data on pitavastatin are scarce. In a recent very small study [21], pitavastatin exerted neutral effects on fasting glucose levels and insulin sensitivity in 2 cohorts of MetS patients [n = 12 from the CAPITAIN (Chronic and Acute effects of PITAvastatIN on monocyte phenotype, endothelial dysfunction and HDL atheroprotective function in patients with MetS) study and n = 9 from the PREVAIL-US (PitavastatincompaREd with praVAstatin In Lowering LDL-C in the USA) study]. Pitavastatin also did not demonstrate any adverse effects with regard to glucose homeostasis in type 2 DM patients [20,22,23] and it was shown to improve glycemic control [24]. A previous analysis of the LIVALO Effectiveness and Safety (LIVES) Study [25] reported improvements in HbA1c levels in type 2 DM patients taking pitavastatin for 104 weeks. In the collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study), atorvastatin (n = 22 patients) was associated with a non-significant increase in HbA1c levels following 12 weeks of therapy, whereas no changes were observed in diabetic patients (n = 23) taking pitavastatin [26]. In patients with impaired fasting glucose or impaired glucose tolerance, both atorvastatin and pitavastatin did not affect glucose metabolism [27].

Although statin use may be linked to an increased risk for NOD, statin-induced reduction in CVD morbidity and all-cause mortality has been reported in both primary and secondary prevention settings [28–30], even in the elderly [31,32]. Data regarding statin-related CVD risk and all-cause mortality reduction in primary prevention studies in women [33–35] may not be as strong but such discrepancies may be attributed to the low representation of women in CVD trials and thus a lack of statistical power [36]. In this context, there has been a scientific debate in the medical community on the use of statins in primary prevention with respect to the risk-benefit ratio especially related to NOD incidence [37,38]. Patients with ≥1 DM risk factors [i.e. MetS, BMI ≥30 kg/m^2, impaired fasting glucose or $HbA1_C$ > 6%] were at a higher risk for statin-related NOD development while experiencing lower CVD risk reduction than those without these factors as reported in an analysis of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) primary prevention study [39]. However, it should be noted that the overall CVD benefits of statin therapy were greater than the hazard of NOD incidence, even in such primary prevention populations [39,40].

With regard to secondary prevention, meta-analyses strongly support that statin-induced CVD risk reduction significantly outweighs the risk of NOD [4,13] and current guidelines recommend the use of statins in such high CVD risk patients [41–44]. Of note, intensive statin therapy (atorvastatin 80 mg) was associated with significantly lower rates of the composite end point (i.e. CVD morbidity, all-cause mortality and revascularization) compared with standard therapy (pravastatin 40 mg) in patients with acute coronary syndromes [45]. Furthermore, a recent meta-analysis highlighted the importance of statin administration prior to percutaneous coronary intervention (PCI) in patients with acute coronary syndromes as compared with statin use after PCI with regard to major adverse cardiac and cerebrovascular events [46]. Also, it is important to keep in mind that statins are effective in patients with type 2 DM in terms of lowering the risk of vascular events [47]. The rates of vascular complications including acute myocardial infarction and stroke have been significantly decreased in diabetic patients in the United States between 1990 and 2010, a finding that can be at least partly attributed to the use of statins in these high-risk individuals [48]. Of note, statin use prior to DM diagnosis was recently reported to be associated with significantly lower cumulative incidences of diabetic retinopathy, neuropathy and foot gangrene compared with non-statin use [49].

It should be noted that, apart from statins, other drugs prescribed for components of the metabolic syndrome may also increase the risk for NOD (e.g. beta-blockers, thiazide diuretics, niacin or steroids) [15,18] or improve insulin sensitivity and/or glucose homeostasis (e.g. angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, colesevelam and even possibly ezetimibe) [50–53].