EDITORIAL (SEE RAJPATHAK ET AL., P. 1924)

Statin-Induced Diabetes: Will It Change Clinical Practice?

An increase in the incidence of physician-diagnosed diabetes with rosuvastatin in Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) published recently revived clinical interest in the effects of statins on glycemic control. The study showed that, after almost 2 years of follow-up in men and women with elevated levels of high-sensitivity C-reactive protein but average LDL cholesterol, rosuvastatin therapy was associated with a mild but significant increase in the identification of new-onset diabetes (3% in the statin arm, 2.4% in the placebo arm; $P < 0.01$) (1). The potential association between statin use and new-onset diabetes gained attention in 2001 when a post hoc analysis of another primary prevention statin trial, the West of Scotland Coronary Prevention Study (WOSCOPS), reported that treatment with pravastatin decreased the hazard of developing type 2 diabetes by 30% (hazard ratio 0.7 [95% CI 0.5–0.99]; $P = 0.042$) (2). These seemingly contradictory findings flank results from four other statin trials that failed to uncover a significant relationship between statin use and incident type 2 diabetes when the latter was evaluated as a tertiary end point (3–6).

In this issue of *Diabetes Care*, Rajpathak et al. (7) bring together six randomized placebo-controlled trials to explore diabetes risk with statins using a meta-analytical approach. The authors found that, if they included all six studies in the analysis (a total of 2,082 cases of incident diabetes in 57,593 study participants), there was no significant association between statin use and the development of type 2 diabetes (relative risk 1.06 [95% CI 0.93–1.25]). On the other hand, when they excluded the WOSCOPS data from the hypothesis-testing meta-analysis, an approach favored by some (8), a small increase in diabetes risk was found (1.13 [1.03–1.23]).

This meta-analysis and one that preceded the results from JUPITER (9) found that inclusion of data from the pravastatin trial(s) introduced statistical heterogeneity. Because of their broader aims, meta-analyses commonly involve trials with differences in treatment regimen, patient characteristics, duration of follow-up, and outcome definition, differences that must be understood to interpret the results adequately (10). Experimental studies in cell culture and animal studies, as well as observations from clinical trials, suggest that there are differences among the various statins on insulin sensitivity and glycemic control, differences that could account for the heterogeneity observed in the meta-analysis (11–14). Important differences in the design of the statin trials analyzed, with varying periods of observation (1.9–6.0 years) and an inconsistent definition of incident diabetes, likely contribute to heterogeneity. Finally, differences in the characteristics of the subjects studied may impact the evaluation of statin-associated metabolic effects (15). In fact, Rajpathak et al. (7) found that sex, but not age, accounted for some of the study's heterogeneity. WOSCOPS was the only one of the six trials analyzed that did not enroll female participants (2). In contrast, 38% of participants in JUPITER were women (1). Differences in overweight and obesity and in the proportion of subjects with impaired fasting glucose across studies also need to be explored because they could well explain the heterogeneity observed in the meta-analysis and account for the differential effect of statins on incident diabetes. For instance, baseline fasting glucose in WOSCOPS averaged 85 mg/dl; in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study, mean fasting glucose was 93.6 mg/dl in subjects with normal glucose tolerance and 113 mg/dl in participants with impaired glucose tolerance (2,5). BMI among subjects in WOSCOPS averaged 25.9 kg/m^2, whereas the mean or median BMI among subjects in the Heart Protection Study (HPS), Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), and JUPITER was above 27 kg/m^2 (1,2,6).

Is the association between statin use and new-onset diabetes plausible? Many mechanistic and experimental studies, mostly with lipophilic statins, support this association. Atorvastatin, but not pravastatin, decreases glucose uptake in adipocyte cell lines (13) and is associated with an increase in A1C in hypercholesterolemic patients (12). Simvastatin, but not pravastatin, was shown to decrease insulin sensitivity and adiponectin levels in a small randomized placebo-controlled study (16). Simvastatin and atorvastatin, but not pravastatin, have been shown to decrease insulin secretion in β-cells (14). On the other hand, a short-term clinical trial comparing rosuvastatin with atorvastatin in subjects with metabolic syndrome showed no significant differences in fasting glucose and in homeostasis model assessment–insulin resistance (HOMA-IR) at 6 weeks between the statins and placebo groups (17). The inhibition of isoprenoid synthesis may explain some of the dysglycemic effects observed with statins (13).

If future studies were to confirm that some or all of the statins are associated with an increased risk for incident diabetes, would it change current clinical practice? Would increases in glycemia be clinically acceptable in the context of the benefit conferred by the use of these medications? We have learned from other trials that improvement of surrogate markers does not necessarily translate into clinical benefit (18). It is well established that in people at increased cardiovascular risk, with and without diabetes, statins provide substantial benefit by decreasing the incidence of major cardiovascular events and overall mortality. Post hoc analyses have suggested that in high-risk subjects without diabetes, it is those with features of the metabolic syndrome who derive a greater benefit from statin use (19).

The development of diabetes is of clinical concern because of the risk of its associated complications. Because cardiovascular disease accounts for almost two-thirds of deaths in people with diabetes, the protective effect of statins on this major complication may suffice to support their use despite a potential risk of new-onset diabetes. What about the effects of statins on microvascular disease? A recent

analysis of more than 345,000 patients in the Veterans Affairs Health Care System (20) showed that statin-induced increases in glycemia were mild. Within a 2-year period of follow-up, fasting plasma glucose increased from 98 to 105 mg/dl in statin users without diabetes and from 97 to 101 mg/dl in their non–statin-using counterparts. In subjects with diabetes, the observed increases were from 102 to 141 mg/dl in statin users and from 100 to 129 mg/dl in nonusers. Although hyperglycemia is strongly associated with the development of microvascular complications, evidence is accumulating to support the notion that dyslipidemia may also play a role and that statins may improve microvascular function (21). Small studies in dyslipidemic patients with diabetes have shown that statins may retard the progression of retinopathy and reduce the severity of hard exudates and subfloveal lipid migration (21–23). Likewise, experimental and clinical studies support an association between dyslipidemia and the progression of renal disease and the benefit of statins on nephropathy (21,24). The evidence for a protective role of statins in neuropathy is more limited but encouraging (25). Overall, there is evidence to suggest that lipid lowering and statin use may have microvascular benefits, but further evidence from randomized controlled trials is needed.

The study by Rajpathak et al. (7) keeps alive the intriguing notion that statins may impact insulin sensitivity and glycemia. As with other meta-analyses, the results are only hypothesis generating because they rely on data published previously and thus are inherently observational. However, and more importantly, the study by Rajpathak et al. brings to our attention how little we know about statins beyond their benefit on macrovascular disease, specifically the need for randomized clinical trials to evaluate the role of statins on microvascular outcomes. If statins reduce macrovascular and microvascular morbidity and mortality, the associated modest increase in glycemia will no longer be an issue of concern.

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