Effect of Extended-Release Niacin on New-Onset Diabetes Among Hyperlipidemic Patients Treated With Ezetimibe/Simvastatin in a Randomized Controlled Trial

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OBJECTIVE—To determine the effect of niacin on fasting glucose (FG) and new-onset diabetes in statin/ezetimibe-treated patients.

RESEARCH DESIGN AND METHODS—This was a prespecified secondary analysis among 942 hyperlipidemic patients randomized to ezetimibe/simvastatin (E/S; 10/20 mg) or E/S + extended-release niacin (N; titrated to 2 g) over 64 weeks.

RESULTS—FG levels peaked by 8–12 weeks, then declined even without antidiabetic medication. At 64 weeks, 3.5% taking E/S+N versus 2.6% taking E/S met criteria for new-onset diabetes (P = 0.66). An additional 1% taking E/S+N versus 0.4% taking E/S transiently met criteria for diabetes and then remitted (P = 0.46). Of 28 new-diabetes diagnoses in the E/S+N group, 25 occurred by 24 weeks. Among patients with baseline diabetes, 13.9% taking E/S+N and 11.6% taking E/S underwent antidiabetic treatment modification.

CONCLUSIONS—Increased FG and new-onset diabetes with E/S+N occurred mainly around the time of initial titration of N and often improved or remitted without specific treatment.

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Figure 1 — Time course of new-onset diabetes and effects on FG. A: Summary of new-onset diabetes. Three pairs of bars on the left compare E/S versus E/S+N groups for patients without diabetes at baseline who developed new-onset diabetes during 0–24 weeks, 24–64 weeks, and cumulatively during 64 weeks. Two pairs of bars on the right enumerate those who developed diabetes and still met criteria for diabetes at study end or transiently met criteria for diabetes, then remitted by 64 weeks (2). Details of patients who met new-onset criteria are described in Supplementary Table 2. B: Frequency of patients who developed new-onset by treatment interval. Mean changes from baseline in FG were generated using an ANCOVA model with terms for treatment and baseline FG during 24 weeks and 24–64 weeks in the full cohort (C), in patients without diabetes at baseline (D) and with diabetes at baseline (E), and those who developed new-onset diabetes (F).

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Fasting glucose levels peaked by 4–8 weeks for E/S and 8–12 weeks for E/S+N, then declined to baseline levels by 64 weeks (Fig. 1C–F). Increases were greatest in those with diabetes at baseline and new-onset diabetes and were higher with E/S+N versus E/S in patients without diabetes (Supplementary Table 4). Among patients with new-onset diabetes, most had peak FG ≥7.0 and ≥8.9 mmol/L (Fig. 1A and Supplementary Fig. 1). During 64 weeks, FG elevations to > 8.9 mmol/L occurred in four patients receiving E/S+N and none receiving E/S. The return to baseline FG levels occurred mostly without antidiabetic medications, which were initiated by only 0.9% on E/S+N vs. 1.3% on E/S (P = 0.70). Among patients with baseline diabetes, 13.9% taking E/S+N over 64 weeks. Most cases of new-onset diabetes occurred within 40 weeks, but was only marginally higher (10.1% in 64 weeks) and/or at high nicinac doses of 3–4.5 g/day (1,8), whereas longer-term studies during the remaining 40 weeks. During 24 weeks, FG elevations occurred at early times with E/S+N, then declined to pretreatment levels by 64 weeks, largely without antidiabetic medications. No trend toward early-onset diabetes was observed with E/S. These effects were not attributed to study treatment adherence, which remained high in both groups through 64 weeks (4).

CONCLUSIONS—The rate of new-onset diabetes with E/S+N therapy was higher compared with E/S during 24 weeks, but was only marginally higher over 64 weeks. Most cases of new-onset diabetes with E/S+N occurred within 24 weeks during nicinac titration to the 2-g dose, with few additional occurrences during the remaining 40 weeks. Similarly, FG elevations occurred at early times with E/S+N, then declined to pretreatment levels by 64 weeks, largely without antidiabetic medications. No trend toward early-onset diabetes was observed with E/S. These effects were not attributed to study treatment adherence, which remained high in both groups through 64 weeks (4).

Our incidence rates for diabetes are somewhat exaggerated due to frequent FG sampling (11 times in 64 weeks) compared with FG monitoring in clinical practice. In addition, 29% of patients meeting criteria for new-onset diabetes on E/S+N remitted by study end. Most cases had incremental FG elevations modestly exceeding 7.0 mmol/L. Nevertheless, the clinical impact of new-onset diabetes for individual patients can be profound. Four patients on E/S+N had destabilization of glucose homeostasis (FG ≥8.9 mmol/L), and 8 of 798 initially nondiabetic patients received antidiabetic medication among both treatment groups.

All new-onset diabetes in this study arose in patients with baseline impaired FG (≥5.6 to < 7.0 mmol/L). Among such patients treated with E/S+N, the rate of new-onset diabetes persisting at 64 weeks was slightly higher (10.1% in 64 weeks) than that suggested for impaired FG in general (25% in 3–5 years) (6). It should be noted that in addition to nicinac, treatment with statins has also been associated with increased development of diabetes (7).

The temporal pattern shown in this article may help explain apparently contradictory results in past studies. Nicinacin-induced hyperglycemia was prominent in studies of short duration (2–12 weeks) and/or at high nicinac doses of 3–4.5 g/day (1,8), whereas longer-term studies during the remaining 40 weeks gave no such evidence (1,12,13). The time course of nicinacin-induced hyperglycemia is interestingly similar to that of skin flushing, which is mediated by a G-protein-coupled receptor, GPR109A, and is subject to desensitization via β-arrestin (14). In humans treated with MK-0354 (a GPR109A agonist that lacks effects on lipoproteins), FG and insulin tended higher (15). Either nicinac or MK-0354 binding to GPR109A strongly inhibits adipocyte triglyceride lipolysis and fatty-acid release, and the resulting perturbation in fuel supply might be linked to increased FG and insulin levels. We speculate that the waning of nicinac’s hyperglycemic effect, analogous to flushing, could be related to potential desensitization of GPR109A on adipocytes.

Our ability to define glycomic responses fully was limited by the study design, optimized to evaluate drug effects on lipids and safety. Characterization of incident diabetes was limited by the small number of cases; nonetheless, the low incidence is reassuring. As with any secondary analysis, these results are considered hypothesis-generating.

In summary, combination E/S+N produced small initial increases in FG and new diagnoses of diabetes that dissipated over time, largely without the use of antidiabetic medication. Consistent with guidelines, nicinac is a reasonable option to treat dyslipidemia in patients with or at risk for diabetes, but risk/benefit should be weighed, and glucose should be checked periodically (2).

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