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Effect of colesevelam and niacin on low-density lipoprotein cholesterol and glycemic control in subjects with dyslipidemia and impaired fasting glucose

Michael H. Davidson, MD, FACC, Michael Rooney, PhD, Elisabeth Pollock, PhD*, Joan Drucker, MD, Young Choy, MS

Preventive Cardiology, The University of Chicago Medicine, Chicago, IL 60637 (Dr Davidson); and Radiant Development, Radiant Research Inc, 515 N. State Street, Suite 2700, Chicago, IL 60654 (Drs Davidson, Rooney, Pollock, Drucker and Ms Choy)

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BACKGROUND: Niacin monotherapy in patients with dyslipidemia and impaired fasting glucose (IFG) may result in hyperglycemia. Colesevelam has the unique dual approvals to lower low-density lipoprotein cholesterol (LDL-C) and to improve glycemic control in type 2 diabetes mellitus.

OBJECTIVES: The aim of our study was to evaluate the effect of combined colesevelam and niacin treatment on LDL-C–lowering and glycemic control in subjects with IFG and dyslipidemia.

METHODS: Men or women ≥ 18 years of age, with dyslipidemia (non–high-density lipoprotein cholesterol ≥ 100 mg/dL and ≤ 220 mg/dL; high-density lipoprotein cholesterol < 60 mg/dL) and fasting plasma glucose (FPG) ≥ 90 mg/dL and ≤ 145 mg/dL were randomly assigned 1:1 to colesevelam (3750 mg/d) with niacin titration (n = 70) or placebo with niacin titration (n = 70) over 12 weeks. Niacin was titrated from 500 mg/d up to a maximum of 2000 mg/d as tolerated, and all subjects took enteric-coated aspirin daily. Lipid and glycemic efficacy parameters were assessed as well as safety evaluations of adverse events, vital signs, alanine aminotransferase, aspartate aminotransferase, hematology, and urinalysis.

RESULTS: Adjunct colesevelam had significantly greater LDL-C–lowering effect than niacin alone (placebo); –20.67% vs −12.86%, respectively (P = .0088). Niacin-mediated increases in FPG were significantly less with adjunct colesevelam (1.8 mg/dL vs 6.7 mg/dL; P = .0046), and fewer colesevelam subjects had increases of ≥10 mg/dL in FPG (8 vs 17, respectively). Adjunct colesevelam resulted in significantly smaller increases in hemoglobin A_{1c} than placebo (0.06% vs 0.18%, respectively; P = .005). Consistent with hemoglobin A_{1c} and FPG changes, fructosamine levels significantly decreased with colesevelam treatment (−5.0 μmol/L) but increased with placebo (3.0 μmol/L; P =.0255).

CONCLUSIONS: Colesevelam as an adjunct to niacin therapy further lowers LDL-C while obviating the adverse effects of niacin on glucose metabolism in patients with dyslipidemia and IFG.

The effects of niacin-induced insulin resistance on glucose control in diabetic patients with dyslipidemia has been reviewed extensively; however, the effect on dyslipidemic subjects with impaired fasting glucose (IFG) is less well characterized.[1–5] The most detailed guidance about the safety of niacin was provided by the National Lipid Association, which stated that glucose increases with niacin therapy are typically in the range of 4% to 5% and that

* Corresponding author.
E-mail address: michaelrooney@radiantresearch.com
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niacin treatment is not contraindicated in patients with diabetes mellitus (DM).[2] In patients with impaired glucose tolerance (IGT) or IFG, the possibility of inducing diabetes may outweigh the cardiovascular benefits of lipid modification. In such patients, niacin-associated insulin resistance is reversible, and the National Lipid Association recommends deferring niacin treatment until glycemic regulation is obtained through lifestyle and dietary interventions.[2]

In patients being treated with niacin for dyslipidemia, high-dose niacin monotherapy (1000-3000 mg nightly) lowers plasma low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs) and raises plasma high-density lipoprotein cholesterol (HDL-C).[6] In both nondiabetic and diabetic subjects with dyslipidemia, niacin raises plasma glucose in a dose-dependent fashion.[1,6–8] Further, in this regard, strong clinical evidence exists that risk of cardiovascular disease jumps significantly when fasting plasma glucose (FPG) is >90 mg/dL, and this occurs even after adjusting the analysis for diabetes, IGT, or IFG.[9–12] Therefore, an increase in plasma glucose levels from niacin administration alone could be a risk in subjects with IFG who are taking niacin for dyslipidemia.

Combination therapy that uses niacin with other lipid-lowering therapies has the potential to improve dyslipidemia while reducing the niacin dose and the undesirable effects on glycemic control. The combination of niacin and bile-acid sequestrants was shown to improve dyslipidemia in subjects with atherosclerotic disease, resulting in significant improvement in the divergence of progression and regression rates of native coronary artery lesions.[13,14] Colesevelam, a bile-acid sequestrant that has significant lipid-lowering effects, is known to decrease plasma glucose in subjects with type 2 DM.[15–19] In 3 randomized, double-blinded, placebo-controlled clinical trials that investigated inadequately controlled type 2 DM, colesevelam reduced hemoglobin A_{1c} (HbA_{1c}) by 0.50% in subjects on sulfonylurea or metformin or both,[16] 0.54%, in subjects on sulfonylurea alone or combined with oral antidiabetes agents,[17] and 0.50% in subjects who receive insulin alone or combined with oral antidiabetes agents.[18]

Because both niacin and colesevelam have lipid-modifying properties, the demonstration of a dual benefit from adjunct treatment of colesevelam in niacin-treated subjects with IFG would be of particular importance, because dyslipidemia considerably accentuates the atherogenic effects of hyperglycemia. A combination therapy with colesevelam and niacin may offer significant advantages over alternative regimens in subjects with both dyslipidemia and potential hyperglycemia. The present study tested the hypothesis that adjunct colesevelam and niacin would effectively treat dyslipidemia in subjects with IFG and, further, would prevent or blunt the elevated plasma glucose levels frequently observed with niacin therapy.

Methods

Study population

Eligible subjects were men or women ≥ 18 years of age, with dyslipidemia (non–HDL-C ≥ 100 mg/dL and ≤ 220 mg/dL), HDL-C < 60 mg/dL, and FPG ≥ 90 mg/dL and ≤ 145 mg/dL.

Study description

Subjects were seen at a screening and a qualifying visit before being randomly assigned to treatment to establish baseline values and to allow for washout of prohibited medications, such as prescription-strength lipid-altering drugs other than statins, medication for DM, type 1 or 2, and glucose-lowering drugs (eg, metformin), drugs that may affect glycemic or lipid control (eg, β-blockers, etc). Use of any weight-loss drugs or cyclic hormones (eg, oral contraceptives and estrogen replacement therapy) during the study was also prohibited. At the randomization visit, subjects were assigned to either placebo or colesevelam (1:1) and took oral colesevelam, 3750 mg, or matching placebo tablets once daily with dinner and liquid during the 12 weeks of treatment. Statin and nonstatin users were randomly assigned from separate randomization schedules, to ensure a balanced distribution of these subjects between the 2 arms. All subjects took niacin tablets daily at bedtime after a low-fat snack and also took 325 mg of enteric-coated aspirin approximately 30 minutes before the niacin dose. The daily dose of niacin started at 500 mg and increased by 500 mg every 2 weeks to 2000 mg at week 6. From week 6 to week 12, subjects continued the 2000 mg dose of niacin or the highest tolerated dose.

Efficacy assessments

The primary efficacy measure, fasting LDL-C, was measured at screening, qualifying, randomization, and the assessment visits (screening and weeks –1, 1, 10, and 12 or early termination [ET]). Secondary efficacy measures of FPG, HDL-C, non–HDL-C, and TGs were measured at the same time points; fructosamine was measured at qualifying, randomization, and the assessment visits (weeks –1, 1, 10, and 12 or ET). Lipoprotein particle counts and size determination were measured by nuclear magnetic resonance (NMR), and the lipoprotein marker-associated insulin resistance (LP-IR) score was calculated at randomization and at the final assessment visit (weeks 1 and 12 or ET). The homeostasis model assessment of insulin resistance (HOMA-IR) was assessed at randomization and the final assessment (week 12 or ET). Insulin was measured by chemoluminescence. Laboratory analyses were done by ACM Global Central Laboratory, Rochester, NY; NMR analyses were done by LipoScience, Inc, Raleigh, NC; fructosamine was measured colorimetrically by Quest Diagnostics, San Juan Capistrano, CA. HbA_{1c} was