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Differential effects of fenofibrate and extended-release niacin on high-density lipoprotein particle size distribution and cholesterol efflux capacity in dyslipidemic patients

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BACKGROUND: The effectiveness of therapies that raise high-density lipoprotein cholesterol (HDL-C) to lower cardiovascular disease risk is currently under debate, and further research into the relationship between HDL-C and function is required.

OBJECTIVE: o investigate whether 2 established HDL-C-raising therapies had differential effects on parameters of high-density lipoprotein (HDL) quality and function, such as HDL particle profile and cholesterol efflux capacity (CEC), in patients with dyslipidemia.

METHODS AND RESULTS: Sixty-six patients with dyslipidemia, 24 with low HDL-C levels (<40 mg/dL) and 42 with normal HDL-C levels (40–59 mg/dL), were treated for 6 weeks with fenofibrate (160 mg/d) or extended-release (ER) niacin (0.5 g/d for 3 weeks, then 1 g/d) with 4 weeks of washout between treatments. Lipoprotein particle size distribution was determined using nuclear magnetic resonance, and pathway-specific serum CECs were assessed in J774 macrophages, hepatoma, and Chinese hamster ovary–human adenosine triphosphate-binding cassette transporter G1 cells. Comparable increases in HDL-C and apolipoprotein A-I levels were seen with fenofibrate and ER niacin. There was a shift toward larger HDL, predominantly to medium-size HDL particles for fenofibrate (+209%) and to large HDL particles for ER niacin (+221%). Minor changes in serum CECs were observed with fenofibrate and ER niacin for all the efflux pathways measured. Small increases in plasma cholesteryl ester transfer protein and lecithin: cholesterol acyltransferase concentrations, and decreases in cholesteryl ester transfer protein activity were seen with both drugs.

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CONCLUSIONS: Fenofibrate and ER niacin increased plasma HDL-C level similarly, but modulated HDL particle size distribution differently; however, these changes did not result in differential effects on serum CECs.

During the past 20 years there have been impressive reductions in coronary heart disease (CHD), mostly because of the extensive use of statins to decrease low-density lipoprotein cholesterol (LDL-C) levels.[1] However, data analyzed from several large statin trials have revealed a significant residual CHD risk despite large reductions in LDL-C levels,[1] suggesting that additional therapeutic options are required to reduce such remaining CHD risk.

Several studies indicated that high-density lipoprotein cholesterol (HDL-C) is an independent inverse predictor of CHD risk.[2,3] Meta-analysis of 4 large prospective studies demonstrated that, for every 1-mg/dL (0.026-mmol/L) increase in plasma HDL-C in the populations studied, CHD risk decreased by around 2% in men and 3% in women,[4] independent of LDL-C levels. A more recent meta-analysis did not confirm previous findings,[5] but small increases in HDL-C levels (<3%) and the variety of HDL-C-raising agents studied could have influenced results.[6] Recent guidelines have encompassed the importance of HDL-C-raising therapy as a secondary therapeutic target. A joint statement by the American Diabetes Association and the American Heart Association advocates a combination of statins with fibrates or extended-release (ER) niacin to target multiple lipids.[7]

Lipid-altering therapies niacin and fenofibrate provide the most effective, currently available means of raising HDL-C levels, although use is limited by modest efficacy and safety and tolerability profile. Niacin—a GPR109a agonist used clinically for more than 50 years to lower cholesterol and triglycerides—as a monotherapy, increases HDL-C levels up to 30%.[8] ER niacin is as effective as niacin in raising HDL-C,[9] and is associated with fewer side effects, especially facial flushing. Fibrates and peroxisome proliferator-activated receptor-α agonists lower triglycerides and raise HDL-C levels by up to 20%, depending on concomitant medication and baseline lipid profile.[10]

HDL-C plasma level, commonly used as a clinical assessment in risk prediction and drug evaluation, is believed to reflect the number of circulating high-density lipoprotein (HDL) particles, and therefore HDL-mediated atheroprotection. However, the HDL family consists of a variety of particles distinct in size, shape, density, and composition that may also differ in atheroprotective ability,[6] and which plasma concentrations might be unrelated to HDL-C level. The atheroprotective ability of HDL is attributed mostly to its capacity to promote cholesterol efflux from lipid-laden macrophages of atheromatous vessels through different pathways, such as passive diffusion (PD), adenosine triphosphate-binding cassette transporter (ABC) A1-mediated efflux, ABCG1-mediated efflux, and scavenger receptor class B type I (SR-BI)-mediated efflux.[11] This cholesterol efflux capacity (CEC), assessed by measuring the ability of apolipoprotein (Apo) B-depleted serum to remove cell cholesterol through standardized in vitro techniques, was found to be related inversely to intima media thickness and coronary artery disease, independent of serum HDL-C level.[12] Therefore, both HDL quality, as reflected by HDL particle profile, and HDL function, as reflected by CEC, for example, represent additional targets for HDL-raising therapies aimed at reducing residual CHD risk in statin-treated patients.[13]

This study was designed to explore the effects of ER niacin and fenofibrate, given to patients with dyslipidemia at equipotent HDL-C-raising doses (half of the maximum recommended dose for ER niacin), on plasma HDL particle profile (a measure of HDL quality) and pathway-specific serum CECs (a measure of HDL function) to investigate the interplay between drug-related increases in HDL-C level and HDL quality and function.

Materials and methods

Patients and trial design

This was a multicenter, open-label, randomized crossover study of male and postmenopausal female patients, with or without prior lipid-lowering therapy, age 18 to 75 years, at low CHD risk, with primary hypercholesterolemia or mixed dyslipidemia, defined by an LDL-C level of >130 mg/dL to <190 mg/dL and a triglyceride level of >135 mg/dL to <440 mg/dL, and with either low (<40 mg/dL) or normal (≥40 mg/dL to <59 mg/dL) HDL-C levels (protocol BP20843). Exclusion criteria and randomization methodology are included in the Supplementary materials. After a 2-week or 6-week period for treatment-naive or lipid-lowering therapy-treated patients respectively, during which any previous lipid-interfering therapy was discontinued, patients were randomized to 1 of 2 treatment sequences: fenofibrate 160 mg/d for 6 weeks per os, or ER niacin 0.5 g/d for 3 weeks followed by 1 g/d for 3 weeks per os (doses anticipated to raise HDL-C to similar levels), with a 4-week washout before being crossed over to the alternative treatment, and a safety follow-up 2 weeks after treatment (Supplementary Fig. I). To confirm a return to baseline values after the first treatment period and washout, lipid parameters at the start of the second treatment period were compared with those from before the first. Healthy