Modulation of HDL-mediated production of nitric oxide by HDL-raising therapies

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Niacin and fenofibrate are to date the most effective available therapies to increase high density lipoprotein-cholesterol (HDL-C) levels. We have recently shown that these two drugs exert different effects on HDL composition/distribution with niacin increasing large HDL containing apoA-I and fenofibrate increasing medium-sized HDL containing both apoA-I and apoA-II. In addition, both drugs increased HDL anti-inflammatory activity in vitro, with niacin being significantly more effective than fenofibrate. Aim of the present study was to investigate the effects of the two HDL-raising drugs on HDL ability to induce nitric oxide (NO) production in endothelial cells.

A multicenter, randomized, open-label, cross-over study was performed on 66 dyslipidemic patients, 24 with low HDL-C levels (36±6 mg/dl) and 42 with normal HDL-C (47±7) mg/dl. Patients received 6 weeks' treatment with niacin extended-release (0.5 g/d then 1.0 g/d) and fenofibrate (160 mg/d), with 4 weeks' wash-out period between the two treatments. HDL were isolated by ultracentrifugation from plasma collected at baseline and after each treatment period. Endothelial cells were incubated with HDL to evaluate the expression of endothelial NO synthase (eNOS) and the production of NO. Niacin and fenofibrate similarly improved HDL ability to induce eNOS expression in endothelial cells (+10% and +11.4%, respectively). In addition, both drugs significantly improved the capacity of HDL to induce NO production (+9% for both drugs). Interestingly, this effect was long-lasting, since it was almost preserved at the end of the 4 weeks' wash-out period between the two treatments and an additional significant 3% increase was observed after the second treatment period.

In conclusion, in patients with a moderate mixed dyslipidemia, the HDL-raising drugs niacin and fenofibrate similarly improved HDL-mediated nitric oxide production in endothelial cells and this effect was preserved after treatment discontinuation.