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Analysis of 6-month effect of orlistat administration, alone or in combination with fenofibrate, on triglyceride-rich lipoprotein metabolism in overweight and obese patients with metabolic syndrome

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Triglycerides

BACKGROUND: Orlistat significantly reduced serum triglycerides (TG) in most clinical trials. Orlistat-induced TG reduction has not been studied to determine the factors contributing to TG alterations in clinical settings.

OBJECTIVE: We examined the factors influencing TG reduction during orlistat administration, alone or in combination with fenofibrate, and we investigated the effects of these treatments on apolipoprotein C-II (ApoC-II) and C-III (ApoC-III) levels.

METHODS: Patients with the metabolic syndrome were randomly allocated to receive orlistat 120 mg three times daily (n = 28, O group), micronized fenofibrate 200 mg/day (n = 28, F group), or both (n = 27, OF group) for 6 months. Plasma ApoC-II and ApoC-III were determined by an immunoturbidimetric assay.

RESULTS: In the O group, we observed reductions of plasma ApoC-III ($P < 0.05$) and ApoC-II (P = NS) levels. Fenofibrate administration significantly reduced concentrations of ApoC-II and ApoC-III, whereas the combination of orlistat and fenofibrate had an additive effect on these apolipoproteins. There were significant in-group reductions in serum TG levels in all treatment groups. Multivariate analysis showed that in O group's baseline TG levels were independently positively correlated, whereas the baseline ApoC-II levels were negatively correlated with TG-lowering. In the F group, baseline TG levels and ApoC-III reduction were significantly and independently correlated with TG reduction. OF group's baseline TG levels and ApoC-III reduction were independently positively correlated and baseline ApoC-II levels were negatively correlated with TG-lowering.

CONCLUSIONS: Orlistat-mediated TG-lowering is independently associated with baseline TG and ApoC-II levels. When orlistat is combined with fenofibrate, ApoC-III reduction is another independent contributor to TG alterations.

Orlistat is the first of a class of antiobesity agents, lipase inhibitors, developed for long-term management of obesity and its associated co-morbidities. When co-administered with diet and exercise, orlistat can help obese patients lose weight.[1] It has been reported that the impact of orlistat on low-density lipoprotein cholesterol (LDL-C) is independent

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of the magnitude of weight loss and is greater in orlistat-treated compared to placebo-treated patients for the same degree of weight loss.[2–4] This independent lipid-lowering effect of orlistat has been studied extensively and attributed to drug-induced reduction in the absorption of dietary fat.[1] Furthermore, in most trials, orlistat significantly reduced serum triglycerides (TG).[4–7] To the best of our knowledge, this orlistat-induced TG reduction has not been studied to determine the factors contributing to TG alterations during orlistat treatment in the clinical setting.

Fibric acid derivatives (fibrates) are lipid-lowering drugs, which mainly exert their actions via activation of specific nuclear receptors called peroxisome proliferator–activated receptors-α (PPAR-α).[8] Fibrates appear to selectively reduce TG-rich lipoproteins.[9] Fenofibrate-induced TG reduction has been associated with alterations of apolipoprotein C-II (ApoC-II) and, especially, ApoC-III.[10–12] ApoC-II is considered an important activator of lipoprotein lipase (LPL) and is required for efficient lipolysis of TG-rich lipoproteins in the circulation.[13,14] ApoC-III consists a powerful inhibitor of LPL activity.[13,15]

In previous studies, we showed that orlistat and fenofibrate, alone or in combination, significantly reduced serum TG concentrations.[16,17] In this study, we show the effect of orlistat administration, alone or combined with fenofibrate, on ApoC-II and ApoC-III levels and we investigate the factors influencing TG reduction during these treatments. To the best of our knowledge, this is the first study examining factors influencing TG metabolism during orlistat monotherapy or in combination with fenofibrate.

Patients and methods

Participants

Consecutive patients attending the Outpatient Obesity and Lipid Clinic of the University Hospital of Ioannina (Ioannina, Greece), who participated in a previous study,[17] were recruited. The study protocol has been described in detail elsewhere.[16–18] Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition.[19] All participants gave their informed consent, and the study protocol was approved by the institutional ethics committee.

Laboratory measurements

Lipid and carbohydrate metabolism parameters were determined as previously described.[16,17] ApoC-II and ApoC-III were determined by an immunoturbidimetric assay provided by Kamiya Biomedical Company (Seattle, WA).[20]

For all measurements in our laboratory, the coefficients of inter- and intra-assay variation were $<5.0\%$, and blinded quality control specimens were included in each assay. Analyses were conducted at the Laboratory of Clinical Chemistry of the University Hospital of Ioannina, under regular quality control procedures, including use of reference pools and blinded duplicate samples.

The Laboratory of the University Hospital of Ioannina is currently participating in External Quality Assurance Services program provided by Bio-Rad Laboratories, Inc. (Hercules, CA).

Statistical analysis

Values are given as mean $\pm$ standard deviation and median (range) for parametric and nonparametric data, respectively. Continuous variables were tested for lack of normality by the Kolmogorov-Smirnov test and logarithmic transformations were accordingly performed. The paired-samples *t*-test was used for assessing the effect of treatment in each group. Analysis of covariance, adjusted for baseline values, was used for comparisons between treatment groups. Spearman's correlation coefficients were used to describe the relationship of TG reduction with age, waist circumference, body weight, body mass index (calculated by dividing weight [kilograms] by height squared [meters squared]), homeostasis model assessment index, lipid and apolipoprotein levels (univariate analysis). Stepwise multivariate linear regression analyses were performed to assess the independent contribution of the variables that were significantly associated with TG reduction in univariate analysis in each treatment group.

Results were analyzed after excluding the six patients who dropped out during the study. Significance was defined as $P < 0.05$. All analyses were carried out with SPSS 15.0 (SPSS Inc., Chicago, IL).

Results

We enrolled 89 patients (19 men and 70 women, mean age 53 $\pm$ 11 years). Six patients dropped out during the study.[17] Baseline characteristics did not differ among the three groups.[17]

As shown previously,[17] significant in-group changes were observed for body mass index, waist circumference, and homeostasis model assessment index at 6 months (Table 1). There were significant in-group reductions in plasma levels of total cholesterol (TC), LDL-C, TG, ApoB, and ApoE. We also observed a significant increase of serum high-density lipoprotein cholesterol (HDL-C) in the fenofibrate (F) group, whereas in the orlistat (O) and OF groups this parameter was not significantly altered.[17]

In the O group, we observed a significant reduction of plasma ApoC-III concentrations (Table 1). In this group plasma ApoC-II levels were decreased, but this reduction did not reach statistical significance ($P = 0.16$). In the F and OF groups, plasma ApoC-II and ApoC-III levels were significantly reduced after the 6-month treatment. The reduction of ApoC-II and ApoC-III levels was significantly