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Combination drug treatment in obese diabetic patients

Theodosios D Filippatos, Moses S Elisaf

Theodosios D Filippatos, Moses S Elisaf, Department of Internal Medicine, University of Ioannina, Ioannina 45110, Greece
Author contributions: Filippatos TD prepared and wrote the editorial; Elisaf MS made corrections and did the final editing of the manuscript.
Correspondence to: Moses S Elisaf, MD, FRSH, FASA, FISA, Professor of Medicine, Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina 45110, Greece. egepi@cc.uoi.gr
Telephone: +30-2651-007509 Fax: +30-2651-007016
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Abstract

Drug combinations that include antiobesity drugs (such as orlistat and sibutramine) and target cardiovascular disease (CVD) risk factors may be a good approach to patients with type 2 diabetes and/or metabolic syndrome (MetS). Our group has investigated the orlistat-fenofibrate combination treatment in obese patients with MetS and the orlistat-ezetimibe and the sibutramine-antihypertensive combination treatment in obese patients with hyperlipidaemia with promising results in CVD risk factor reduction. In these studies, the combination treatment significantly improved the lipid and lipoprotein profile, the carbohydrate metabolism parameters and many other variables playing a role in the atherosclerotic process. Small studies give promising results but double-blind, randomized trials examining the effects of such multifactorial treatment in hard CVD endpoints in diabetic or MetS patients are missing.

Key words: Diabetes; Metabolic syndrome; Orlistat; Sibutramine; Fenofibrate; Ezetimibe; Weight loss

Peer reviewer: Suresh Mathews, PhD, Assistant Professor, Department of Nutrition and Food Sciences, 260 Lem Morrison Dr., 101 PSB, Auburn University, Auburn, AL 36849, United States

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INTRODUCTION

The prevalence of metabolic syndrome (MetS) and type 2 diabetes (T2DM) is increasing and expected to rise in the next decade[1-3]. Visceral obesity and insulin resistance (IR) play a central role in the pathogenesis of these conditions[4]. IR results in hyperinsulinaemia and high levels of plasma free fatty acids which enter into the hepatocyte cytoplasm, resulting in the overproduction of very low density lipoprotein cholesterol (VLDL) particles by the liver[5]. In patients with increased VLDL concentration (such as patients with MetS and T2DM), the cholesterol esters in low density lipoprotein (LDL) particles are exchanged for triglycerides (TGs) in VLDL by the cholesterol ester transfer protein. Then, triglycerides in LDL are hydrolyzed by hepatic lipase, producing small dense low density lipoprotein cholesterol (sdLDL) particles[5]. Our group has shown that subjects with MetS exhibit significantly higher concentrations of the atherogenic sdLDL subfractions compared with non MetS individuals[6]. Previous studies have reported a linear correlation between the concentration of sdLDL particles and the risk for the development of cardiovascular events[7-9].

Diabetic patients have increased cardiovascular disease (CVD) morbidity and mortality which are in part associated with the high prevalence of visceral obesity, dyslipidemia and hypertension in this population[10]. These patients may require a multifactorial approach targeting excess body weight and CVD risk factors to reduce CVD events. In this context, combinations of antiobesity drugs (such as orlistat and sibutramine)

and drugs that target CVD risk factors may offer an approach to lower cardiometabolic risk in such patients.

STUDIES INCLUDING ORLISTAT

Orlistat is an anti-obesity drug with a well documented efficacy in weight reduction and maintenance[11-13]. The drug also has beneficial effects on metabolic indices, reducing the incidence of T2DM in patients with impaired glucose tolerance[12-15]. It was also shown to decrease LDL-C levels to a greater degree than expected from weight loss alone[12,13]. In obese patients with hypercholesterolaemia, orlistat - fluvastatin, orlistat - simvastatin and orlistat - cerivastatin combinations led to pronounced weight loss and a greater decrease in LDL-C concentration compared with statin monotherapy[16-18].

Our group assessed in an open-label randomized study (the FenOrli study) the effect of orlistat and fenofibrate combination in overweight and obese patients (n = 89) with MetS [defined as having 3 of the following 5 criteria: waist circumference ⩾ 102 cm in men or ⩾ 94 cm in women, blood pressure ⩾ 130/85 mmHg (or antihypertensive treatment), HDL-C ⩽ 40 mg/dL in men or ⩽ 50 mg/dL in women, TG ⩾ 150 mg/dL, glucose ⩾ 126 mg/dL or antidiabetic treatment][19]. At the end of the 6-mo treatment period only 54% of patients in the orlistat group, 46% in the fenofibrate group and 29% in the combination group still met the MetS diagnostic criteria ($P < 0.01$ *vs* baseline in all treatment groups)[20]. At 6 mo significantly greater reduction was observed in body weight, body mass index (BMI) and waist circumference in groups receiving orlistat[20]. There were significantly greater reductions in plasma levels of total cholesterol (TC), LDL cholesterol (LDL-C) and TGs in the combination group compared with monotherapy. Glucose, insulin and homeostasis model assessment (HOMA) index levels were improved after the 6-mo treatment significantly more in groups receiving orlistat compared with fenofibrate monotherapy. We also observed significant reductions in blood pressure in all treatment groups[20]. Furthermore, at 6 mo fenofibrate and combination treatment groups experienced a greater reduction in sdLDL-C levels (-63% and -77% respectively) along with a greater increase in LDL particle diameter compared with orlistat monotherapy (-35%, $P < 0.05$ for both)[20], a result which may be clinically relevant since sdLDL particles are considered the most atherogenic[9]. No significant alteration of small or large HDL-C plasma levels occurred with combined orlistat-fenofibrate treatment[21].

Our group also investigated the effects of orlistat and ezetimibe combination in an open-label randomized trial in 86 overweight and obese patients with hypercholesterolemia[22]. Significantly greater reductions were observed for BMI, waist circumference and body weight at 6 months in groups receiving orlistat compared with ezetimibe monotherapy. At the end of the 6-mo treatment period, significant reductions in LDL-C levels were observed in all groups. The fall in LDL-C concentration was significantly greater in the combination group compared with either monotherapy[22]. We also observed greater reductions in TC and TG concentration in the combination group compared with monotherapy. Glucose, insulin and HOMA index levels were improved after the 6-mo treatment significantly more in groups receiving orlistat. We also observed significant reductions in BP in groups receiving orlistat. The sdLDL-C concentration was reduced significantly more in the combination group compared with both monotherapies. In the orlistat-ezetimibe combination, HDL-2 subclass did not significantly change while the cholesterol concentration of HDL-3 subclass decreased significantly[23].

STUDIES INCLUDING SIBUTRAMINE

Sibutramine is another antiobesity drug with a well established efficacy in weight reduction and maintenance of weight loss[24]. Weight loss with sibutramine treatment has been associated with an improvement of insulin sensitivity and a favorable lipid profile[25]. In a recent study we examined the effect of sibutramine together with verapamil slow release/trandolapril (VeTra) combination tablet *vs* VeTra alone in obese hypertensive patients[26]. The combination treatment resulted in greater reductions of BP (significant only for diastolic BP) compared with the antihypertensive treatment alone at 6 mo with no significant change in heart rate in any group[26]. Significant reductions in body weight, BMI and waist circumference were observed in both groups during the first 3 mo but only in the SiVeTra group at the end of the study. Significant reductions were noted in insulin levels and HOMA index in both groups but they were greater in the SiVeTra group compared with the VeTra group. We observed significant reductions in TC, TGs and LDL-C only in the SiVeTra group (all $P < 0.05$ *vs* VeTra group). Subfraction analysis of LDL and HDL particles was only performed in the SiVeTra group and showed a significant decrease in sdLDL-C concentration but no significant change in HDL particle distribution during treatment. Additionally, pre-beta1-HDL levels, a precursor of HDL particles, did not change significantly in the SiVeTra group. We observed significant reductions in visfatin (an adipokine related with atherosclerotic diseases[27]) and high sensitivity C-reactive protein plasma levels at the end of the 6-month treatment in the SiVeTra group.

STUDIES INCLUDING RIMONABANT

We also showed successful results in reversing metabolic syndrome in obese patients with MetS receiving combination of fenofibrate and the recently withdrawn rimonabant[28]. The combination treatment resulted in a significantly more pronounced reduction in the number of metabolic syndrome criteria compared with fenofibrate monotherapy ($P < 0.05$)[28].

CONCLUSION

Taken together, these data suggest that combination treatment that includes a weight loss drug helps to improve lipoprotein profile, carbohydrate metabolism variables, hypertension and many other CVD risk factors or markers. Furthermore, this combination treatment reduced the presence of MetS criteria in obese patients with MetS.

These results are promising for patients with obesity and MetS. These patients need a multifactorial treatment targeting excess body weight, hyperlipidaemia and hypertension to reduce CVD risk factors. Though the population size was small, promising results from these findings indicate a need for double-blind, randomized trials examining the effects of such multifactorial treatment in hard CVD endpoints in patients with T2DM.

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