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

Received: October 9, 2009 Revised: February 20, 2010

Accepted: February 27, 2010

Published online: March 15, 2010

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.

© 2010 Baishideng. All rights reserved.

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

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 hypercholesterolemia, 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 \[^{[19]}\] 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), LDL-C ≤ 40 mg/dL in men or ≤ 50 mg/dL in women, TG ≥ 150 mg/dL, glucose ≥ 126 mg/dL or antidiabetic treatment\[^{[20]}\]. 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 \(^P<0.01\) \[^{[20]}\]. 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 BP in all treatment groups\[^{[21]}\]. At 6 mo significantly greater reduction was observed 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\[^{[21]}\].

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 ezetimibe 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 \(\text{vs}\) 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 \((\text{all} P < 0.05\) \[^{[26]}\]). 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.

REFERENCES

1 Athyros VG, Ganotakis ES, Elisaf M, Mikhailidis DP. The prevalence of the metabolic syndrome using the National Cholesterol Educational Program and International Diabetes Federation definitions. Curr Med Res Opin 2005; 21: 1157-1159.
2 Athyros VG, Ganotakis ES, Bathianaki M, Monedas I, Goudevenos IA, Papageorgiou AA, Papathanasiou A, Kakafika AI, Mikhailidis DP, Elisaf M. Awareness, treatment and control of the metabolic syndrome and its components: a multicentre Greek study. Hellenic J Cardiol 2005; 46: 380-386.
3 Athyros VG, Bouloukos VI, Pehlivanidis AN, Papageorgiou AA, Dionysopoulou SG, Symeonidis AN, Petridis DI, Kapoutsouzi MI, Satsoglou EA, Mikhailidis DP. The prevalence of the metabolic syndrome in Greece: the MetS-Greece Multicentre Study. Diabetes Metab 2005; 7: 397-405.
4 Daskalopoulou SS, Mikhailidis DP, Elisaf M. Prevention and treatment of the metabolic syndrome. Angiology 2004; 55: 589-612.
5 Adeli K, Taghibiglou C, Van Idsman SC, Lewis GF. Mechanisms of hepatic very low-density lipoprotein overproduction in insulin resistance. Trends Cardiovase Med 2001; 11: 170-176.
6 Gazi I, Tsimihodimos V, Filipatos T, Bairaktari E, Tselipe AD, Elisaf M. Concentration and relative distribution of low-density lipoprotein subfractions in patients with metabolic syndrome defined according to the National Cholesterol Education Program criteria. Metabolism 2006; 55: 885-891.
7 St-Pierre AC, Cantin B, Dagenais GR, Maunierge P, Bernard PM, Després JP, Lamarche B. Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Québec Cardiovascular Study. Arterioscler Thromb Vasc Biol 2005; 25: 533-539.
8 Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. JAMA 1996; 276: 875-881.
9 Gazi I, Tsimihodimos V, Tselipe AD, Elisaf M, Mikhailidis DP. Clinical importance and therapeutic modulation of small dense low-density lipoprotein particles. Expert Opin Biol Ther 2007; 7: 53-72.
10 Athyros VG, Mikhailidis DP, Papageorgiou AA, Didangelos TP, Ganotakis ES, Symeonidis AN, Daskalopoulou SS, Kakafika AI, Mikhailidis M. Prevalence of atherosclerotic vascular disease among subjects with the metabolic syndrome with or without diabetes mellitus: the METS-GREECE Multicentre Study. Curr Med Res Opin 2004; 20: 1691-1701.
11 Filipatos T, Derdemezis C, Elisaf M. Effects of orlistat, alone, or combined with hypolipidemic drugs, on cardiovascular risk factors. Clin Lipidol 2009; 4: 331-341.
12 Torgerson JS, Hauptman J, Boldrin MN, Sjöstöm L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004; 27: 155-161.
13 Kiortsis DN, Filipatos TD, Elisaf MS. The effects of orlistat on metabolic parameters and other cardiovascular risk factors. Diabetes Metab 2005; 31: 15-22.
14 Filipatos TD, Mikhailidis DP. Lipid-lowering drugs acting at the level of the gastrointestinal tract. Curr Pharm Des 2009; 15: 590-516.
15 Filipatos T, Tsimihodimos V, Kostapanos M, Kostara C, Bairaktari E, Kiortsis D, Elisaf M. Analysis of the 6-month effect of orlistat, alone or in combination with fenofibrate, administration on triglyceride-rich lipoprotein metabolism in overweight and obese patients with hypercholesterolaemia prescribed a standardized diet. Clin Ther 2003; 25: 1107-1122.
16 Derosa G, Mugellini A, Ciccarelli L, Fogari R. Randomized, double-blind, placebo-controlled comparison of the action of orlistat, fluvastatin, or both an anthropometric measurements, blood pressure, and lipid profile in obese patients with hypercholesterolaemia prescribed a standardized diet. Clin Ther 2003; 25: 1107-1122.
17 Derosa G, Mugellini A, Ciccarelli L, Rinaldi A, Fogari R. Effects of Orlistat, Simvastatin and Orlistat+Simvastatin in Obese Patients with Hypercholesterolemia: A Randomised, Open-Label Trial. Curr Ther Res Clin Exp 2002; 63: 621-633.
18 Derosa G, Mugellini A, Fogari R. Comparison between diet, orlistat and cerivastatin in hypercholesterolemic, obese patients, with mild hypertension [Abstract]. Atheroscle Suppl 2001; 2: 93.
19 Filipatos TD, Kiortsis DN, Liberopoulos EN, Georgoula M, Mikhailidis DP, Elisaf MS. Effect of orlistat, micronised fenofibrate and their combination on metabolic parameters in overweight and obese patients with the metabolic syndrome: the FenOrli study. Curr Med Res Opin 2005; 21: 1997-2006.
20 Filipatos TD, Gazi IF, Liberopoulos EN, Athyros VG, Elisaf MS, Tsetlepis AD, Kiortsis DN. The effect of orlistat and fenofibrate, alone or in combination, on small dense LDL and lipoprotein-associated phospholipase A2 in obese patients with metabolic syndrome. Atherosclerosis 2007; 193: 428-437.
21 Filipatos TD, Liberopoulos EN, Kostapanos M, Gazi IF, Papavasiliou EC, Kiortsis DN, Tsetlepis AD, Elisaf MS. The effects of orlistat and fenofibrate, alone or in combination, on high-density lipoprotein subfractions and pre-beta1-HDL levels in obese patients with metabolic syndrome. Diabetes Obes Metab 2008; 10: 476-85.
22 Nakou ES, Filipatos TD, Georgoula M, Kiortsis DN, Tsetlepis AD, Mikhailidis DP, Elisaf MS. The effect of orlistat and ezetimibe, alone or in combination, on serum LDL and small dense LDL cholesterol levels in overweight and obese patients with hypercholesterolaemia. Curr Med Res Opin 2008; 24: 1919-1929.
23 Nakou ES, Filipatos TD, Kiortsis DN, Derdemezis CS, Tsetlepis AD, Mikhailidis DP, Elisaf MS. The effects of ezetimibe and orlistat, alone or in combination, on high-density lipoprotein (HDL) subclasses and HDL-associated enzyme activities in overweight and obese patients with hyperlipidaemia. Expert Opin Pharmacother 2008; 9: 3151-3158.
24 James WP, Astrup A, Finer N, Hilsted J, Kopelman P, Rossner S, Sarsis WH, Van Gaal LF. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. Lancet 2000; 356: 2119-2125.
25 Filipatos TD, Kiortsis DN, Liberopoulos EN, Mikhailidis DP, Elisaf MS. A review of the metabolic effects of sibutramine. Curr Med Res Opin 2005; 21: 457-468.
Filippatos TD et al. Combination treatment in diabetes

26 Nakou E, Filippatos TD, Liberopoulos EN, Tselepis AD, Kiortsis DN, Mikhailidis DP, Elisaf MS. Effects of sibutramine plus verapamil sustained release/trandolapril combination on blood pressure and metabolic variables in obese hypertensive patients. Expert Opin Pharmacother 2008; 9: 1629-1639

27 Filippatos T, Randeva H, Derdemezis C, Elisaf M, Mikhailidis D. Visfatin/pbeif and atherosclerosis-related diseases. Curr Vasc Pharmacol 2009; In press.

28 Florentin M, Liberopoulos EN, Filippatos TD, Kostara C, Tselepis A, Mikhailidis DP, Elisaf M. Effect of rimonabant, micronised fenofibrate and their combination on cardiometabolic risk factors in overweight/obese patients: a pilot study. Expert Opin Pharmacother 2008; 9: 2741-2750