

Open-label study for the comparison of metabolic effects of orlistat and sibutramine in women participating in an Obesity management program

Obezite tedavi programında yer alan kadınlarda orlistat ve sibutraminin metabolik etkilerinin karşılaştırıldığı açık etiketli bir çalışma

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Abstract

Objective: Both orlistat and sibutramine are anti-obesity drugs with a well-documented efficacy in weight reduction. The aim of present study was to assess comparatively the influence of obesity pharmacotherapy (orlistat or sibutramine) in an obesity management program on anthropometric variables, lipid profile, insulin sensitivity, hemostatic and inflammatory markers, liver function tests and homocysteine levels.

Materials and Methods: This study enrolled 90 obese women (46 in orlistat group and 44 in sibutramine group) who completed a 6-months' weight-reduction program.

Results: Orlistat- and sibutramine-treated patients achieved significant weight loss (9.5 ± 6.9 kg in the orlistat group and 11.9 ± 7 kg in the sibutramine group vs. baseline; $P < 0.001$). Both treatment-induced weight-loss interventions resulted in significant improvement in lipid profile, fasting insulin as well as the HOMA index as a measure of insulin resistance. Reductions in C-reactive protein and D-dimer levels, but not in those of fibrinogen were also noted. Of the liver function parameters, AST and -GGT ($P < 0.001$ for both groups), but not ALT levels decreased significantly during treatment. Notably, serum homocysteine levels were increased significantly at the end of the treatment period.

Conclusion: Short-term therapy with either sibutramine or orlistat in an obesity management program resulted in clinically significant weight loss in obese women. The weight loss was paralleled by a favorable metabolic profile except for an increase in homocysteine levels. Both drugs were well tolerated. *Turk Jem 2007; 11: 54-8*

Key words: Sibutramine, orlistat, weight reduction, lipid, insulin sensitivity, hemostatic, inflammatory markers, liver function tests, homocysteine

Özet

Amaç: Orlistat ve sibutramin, obezite tedavisinde kilo kaybı sağlamada etkinlikleri iyi bilinen ilaçlardır. Bu çalışmada amaç, obezite tedavi programı dahilinde kullanılan farmakoterapinin (orlistat ve sibutramin), antropometrik değişkenler, lipid profili, insulin direnci, hemostatik ve inflamatuvar belirteçler, karaciğer fonksiyon testleri ve homosistein seviyeleri üzerine etkilerini karşılaştırmalı olarak araştırmaktır.

Gereç ve Yöntem: Bu çalışmaya 6-aylık kilo kaybı tedavi programını tamamlayan 90 obez kadın hasta (orlistat grubunda 46 hasta, sibutramin grubunda 44 hasta) dahil edildi.

Bulgular: Orlistat ve sibutramin ile tedavi edilen hastalarda anlamlı kilo kaybı sağlandı (Orlistat grubunda 9.5 ± 6.9 kg, sibutramin grubunda 11.9 ± 7 , başlangıç ve çalışma sonu; $P < 0.001$). Her iki ilaç tedavisi lipid profilinde, açlık insulin seviyesinin yanı sıra insulin direncinin bir göstergesi olan HOMA indeksinde anlamlı düzelme sağladı. C-reaktif protein ve D-Dimer seviyelerinde anlamlı azalma saptanırken, fibrinojen düzeyinde değişiklik saptanmadı. Karaciğer fonksiyon testlerinde, AST ve GGT düzeylerinde anlamlı azalma saptanırken ($P < 0.001$, her iki ilaç için), ALT seviyesinde tedavi sonrası değişiklik saptanmadı. İlginç olarak, serum homosistein seviyesi tedavi sonrası anlamlı artış gösterdi.

Sonuç: Obezite tedavi programında yer alan kadınlarda, kısa süreli orlistat veya sibutramin tedavisi ile anlamlı kilo kaybı sağlandı. Kilo kaybı, homosistein değerinde artış dışında, metabolik profilde anlamlı düzelme sağladı. Her iki ilaç iyi tolere edildi. *Turk Jem 2007; 11: 54-8*

Anahtar kelimeler: Sibutramin, orlistat, kilo kaybı, lipid, insulin duyarlılığı, hemostatik, inflamatuvar belirteçler, karaciğer fonksiyon testleri, homosistein

Introduction

Obesity is associated with metabolic, hormonal, neuroendocrine, hemostatic and inflammatory abnormalities. Further, it is an independent risk factor for death from coronary heart disease. Central obesity increases a person's risk of developing conditions such as insulin resistance, hypertension, hyperlipidemia, fatty liver and atherogenesis (1-3). Weight reduction leads to positive change in or elimination of most of these obesity-related risk factors and co-morbid conditions (4,5).

Clearly, there is a need to establish the most effective weight loss strategy for obese patients. Medications are useful adjuncts to diet and exercise, and may help patients lose weight and maintain substantially reduced weight (6-8). Orlistat inhibits gastrointestinal lipases and, as such, prevents the absorption of dietary fat. Sibutramine, a potent inhibitor of noradrenaline and serotonin reuptake, inhibits food intake and is believed to stimulate thermogenesis. Data have shown that each of these agents, when used in combination with a hypocaloric diet and exercise prescription, helps reduce weight in obese patients (9). Further, it has been shown that such orlistat or sibutramine regimens have a positive effect on metabolic parameters and reduce or eliminate other cardiovascular risk factors (10).

The purpose of this study was to compare the effects of orlistat versus sibutramine in women enrolled in an obesity management program. Specifically, we examined changes in anthropometric variables, body composition, lipid profile, insulin sensitivity, hemostatic and inflammatory markers, and serum levels of liver enzymes and homocysteine.

Materials and Methods

This prospective, observational cohort study was conducted on women who were enrolled in an obesity outpatient clinic. Our institutional research ethics committee approved the study protocol, and informed consent was obtained from each participant. The inclusion criteria were age 18 to 65 years and body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters ≥ 30 kg/m². Patients were excluded if they exhibited endocrine obesity, hypercortisolism, thyroid dysfunction, diabetes mellitus, pregnancy and lactation, hepatic or renal dysfunction, history of heart failure, stroke or ischemic heart disease or significant neurological or psychological illness (depression, epilepsy, schizophrenia). The other exclusion criteria were resting pulse rate > 100 beats/minute; systolic blood pressure > 150 mmHg and diastolic blood pressure > 100 mmHg; > 3 kg weight change in the 3 months prior to the study; malignancy, or alcohol or drug abuse. Before starting the study, each woman underwent an initial assessment that included collection of medical history, physical examination, a 12-lead electrocardiogram, and determination of height, weight and BMI. A blood sample was obtained to measure serum concentrations of fasting glucose and insulin, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides. Insulin resistance was estimated based on calculation of the homeostasis model assessment (HOMA) index for each patient. This was done using the formula,

(Fasting Plasma Insulin [μU/ml] x Fasting Plasma Glucose [mmol/L]) \div 22.5.

Serum levels of D-dimer, fibrinogen, C-reactive protein (CRP), and homocysteine were measured as hemostatic and inflammatory markers. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT) were measured as indicators of liver function.

Each subject's fat mass, percentage body fat (%BF), and free fat mass were recorded using a body composition analyzer (Tanita TBF-300, Tanita Corp., Tokyo, Japan). The Tanita TBF-300 is a commercially available foot-to-foot bioelectrical impedance analysis system. The manufacturer-supplied equations incorporate sex, mass, height, activity category and a measured impedance value to determine %BF and fat mass values.

After the baseline assessment was completed, each participant was randomly assigned to receive orlistat (120 mg 3 times daily, 1 tablet before each meal) or sibutramine (10 mg daily). Each woman completed initial nutrition education classes which included a face-to-face interview with a dietitian and group obesity education program. A written meal plan that provided a low-calorie diet with an estimated 500 kcal/day dietary deficit was prescribed, and individuals were encouraged to increase their physical activity by walking briskly for 30 to 45 minutes 3 to 5 times per week.

Two follow-up visits were scheduled at 3-month intervals. Clinical and laboratory parameters were recorded before the study (at the initial assessment) and at 6 months. The women were questioned about adverse effects during an interview at each control visit. A total of 90 obese women completed the 6-month treatment protocol. The characteristics of the patient population at study entry were similar in the two treatment groups (Table 1).

Methods for blood testing

Each venous sample was drawn after a minimum fasting period of 12 hours. All samples were collected between 0800 and 0900 hours. Serum glucose was measured by the glucose oxidase technique (Roche Diagnostics GmbH, Mannheim, Germany), with an inter-assay coefficient of variation (CV) of 1.8% and an intra-assay CV of 0.9%. Insulin levels were measured by microparticle enzyme immunoassay (Abbott, Weisbaden-Delkenheim, Germany) with inter-assay and intra-assay CVs of 2.5%. Total cholesterol, HDL-C, and triglyceride concentrations were measured by enzymatic assay (Boehringer, Mannheim, Germany). LDL-C was calculated using Friedewald's formula [LDL-C = total cholesterol - (HDL-C + triglyceride/5)]. Serum CRP levels were determined using an immunonephelometry system, according to the manufacturer's instructions (Dade Behring, BCT, Marburg, Germany). Serum homocysteine was measured by fluorescence polarization immunoassay (Abbott, Germany). Serum fibrinogen was measured by clotting assay (Diagnostica Stago, Asnieres-Sur-Seine, France), with an inter-assay CV of 3.6% and an intra-assay CV of 3.9%. D-Dimer levels were determined by latex agglutination (D-dimer Plus commercial kit, Dade Behring BCT). Serum levels of ALT, ASP, GGT, alkaline phosphatase and bilirubin were measured in a 24-factor automated chemical analyzer using standard reagents.

Statistical analysis

All continuous data were expressed as mean \pm SD. Data analysis was done using the Statistical Package for the Social Sciences (SPSS for Windows version 10.0; SPSS Inc., Chicago, IL, USA). P values < 0.05 were considered statistically significant. Paired t tests were used to assess parameter changes that occurred with the two different weight loss protocols.

Results

As noted, a total of 90 women (46 in the orlistat group and 44 in the sibutramine group) completed the 6-month obesity therapy program. Table 1 shows the group findings at baseline and at 6 months (end of program) for demographic and anthropometric variables, body composition, lipid profile, insulin resistance, hemostatic and inflammatory markers, liver enzyme levels, and homocysteine levels.

There were no significant differences between the orlistat group and the sibutramine group with respect to age (40.9 ± 11.5 years vs. 42.4 ± 10.1 years, respectively; $P > 0.05$) or initial body weight (96.5 ± 11.9 kg vs. 95.4 ± 10.5 kg, respectively; $P > 0.05$).

Weight loss and changes in body composition

Both treatment groups showed highly significant improvements in body weight, BMI, and waist circumference after 6 months on the program. The mean weight loss noted for the orlistat group was 9.5 ± 6.9 kg, and that for the sibutramine group was 11.9 ± 7 kg. The orlistat group dropped from 96.5 ± 11.9 kg to 87 ± 11.9 kg, and the sibutramine group dropped from 95.4 ± 11.5 kg to 83.5 ± 10.4 kg ($P < 0.001$ for both). The orlistat group's mean BMI fell from 39.1 ± 5 kg/m² to 35.2 ± 4.9 kg/m², and the sibutramine group's mean BMI fell from 39.5 ± 4.8 kg/m² to 34.5 ± 4.27 kg/m² ($P < 0.001$ for both). Mean waist circumference in the orlistat group decreased from 105.1 ± 8.5 cm to 99.1 ± 7.1 cm, and that in the sibutramine group decreased from 105.6 ± 9.2 cm to 97.9 ± 7.6 cm ($P < 0.001$ for both).

There were no significant differences between the two groups with respect to change in weight, reduction in BMI, or decrease in waist circumference during the study.

Both groups showed significantly reduced fat mass (41.7 ± 7.9 kg at baseline vs. 34.6 ± 6.8 kg at 6 months in the orlistat group [$P < 0.001$]; 42.8 ± 8.7 kg vs. 34.3 ± 7 kg, respectively, in the sibutramine group [$P < 0.001$]). Both groups also showed significantly lower %BF ($43.8 \pm 4.9\%$ vs. $39.5 \pm 4.4\%$, respectively, for the orlistat group [$P < 0.001$]; $45.3 \pm 4.3\%$ vs. $40.3 \pm 4.1\%$, respectively, for the sibutramine group [$P < 0.001$]).

Metabolic changes

Mean fasting insulin levels and mean HOMA index values (indicating degree of insulin resistance) improved significantly in both groups (from 4.1 ± 2.9 to 3 ± 2.8 in the orlistat group, and from 4.3 ± 2.9 to 2.9 ± 1.7 in the sibutramine group; $P < 0.001$ for both). However, neither group showed a significant change in mean fasting glucose level ($P > 0.05$ for both). Both groups showed significant reductions from baseline to the 6-month assessment for three of the lipid parameters: total cholesterol from 205 ± 30.8 mg/dL to 189.9 ± 28.3 mg/dL with orlistat, and from 198.3 ± 33.2 mg/dL to 188.1 ± 30.1 mg/dL with sibutramine ($P < 0.001$ for both); LDL-C from 126.3 ± 26.6 mg/dL to 111 ± 24.6 mg/dL with orlistat, and from 122.3 ± 28.8 to 110.7 ± 24.3 mg/dL with sibutramine ($P < 0.001$ for both); triglyceride from 146.6 ± 56.2 mg/dL to 130.5 ± 49.1 mg/dL with orlistat, and from 145.3 ± 52.1 mg/dL to 128.8 ± 46.9 mg/dL with sibutramine ($P < 0.001$ for both). There was a significant rise in HDL-C in

Table 1. Data for anthropometric, body composition, metabolic parameters, and liver function tests in the orlistat and sibutramine-treated groups before and after therapy. Data are mean \pm SD

	Orlistat (n = 46)			Sibutramine (n = 44)		
	Before	After	P	Before	After	P
Weight (kg)	96.5 \pm 11.9	87 \pm 11.9	< 0.001	95.4 \pm 11.5	83.5 \pm 10.4	< 0.001
BMI (kg/m ²)	39.1 \pm 5	35.2 \pm 4.9	< 0.001	39.5 \pm 4.8	34.5 \pm 4.27	< 0.001
WC (cm)	105.1 \pm 8.5	99.1 \pm 7.1	< 0.001	105.6 \pm 9.2	97.9 \pm 7.6	< 0.001
Body fat (%)	43.8 \pm 4.95	39.5 \pm 4.4	< 0.001	45.3 \pm 4.3	40.3 \pm 4.1	< 0.001
Fat mass (kg)	41.7 \pm 7.9	34.6 \pm 6.8	< 0.001	42.8 \pm 8.7	34.3 \pm 7	< 0.001
Free fat mass (kg)	52.9 \pm 9.7	52.6 \pm 7.6	> 0.05	50.3 \pm 7.1	50.2 \pm 5.4	> 0.05
FPG (mg/dL)	96.5 \pm 18.5	100.1 \pm 12.6	> 0.05	99.9 \pm 18.5	100.7 \pm 11.6	> 0.05
FPI (pmol/L)	15.9 \pm 8.1	11.2 \pm 5.4	< 0.001	16.6 \pm 8.2	11.2 \pm 6	< 0.001
HOMA index	4.1 \pm 2.9	3 \pm 2.8	< 0.001	4.3 \pm 2.9	2.9 \pm 1.7	< 0.001
Total-C (mg/dL)	205 \pm 30.8	189.9 \pm 28.3	< 0.001	198.3 \pm 33.2	188.1 \pm 30.1	0.012
LDL-C (mg/dL)	126.3 \pm 26.6	111 \pm 24.6	< 0.001	122.3 \pm 28.8	110.7 \pm 24.3	0.005
HDL-C (mg/dL)	49.6 \pm 10.9	55.5 \pm 12.2	< 0.001	47.2 \pm 9.3	54.9 \pm 8.6	< 0.001
TG (mg/dL)	146.6 \pm 56.2	130.5 \pm 49.1	< 0.001	145.3 \pm 52.1	128.8 \pm 46.9	0.001
AST (IU/L)	26.6 \pm 6.6	21.7 \pm 10.8	0.003	27.4 \pm 7.2	21.7 \pm 11.1	0.001
ALT (IU/L)	22.4 \pm 12.9	22.9 \pm 15.4	> 0.05	23.3 \pm 12.7	22.1 \pm 16.7	> 0.05
GGT(IU/L)	22.3 \pm 6.1	17.3 \pm 6.1	< 0.001	22.4 \pm 7.2	17 \pm 6.4	< 0.001
CRP (mg/L)	6.1 \pm 4.7	4.2 \pm 2.7	< 0.001	7.2 \pm 4.8	4.9 \pm 2.4	< 0.001
Homocysteine (μ mol/L)	10 \pm 2.2	11.8 \pm 3.7	< 0.001	10.5 \pm 3	12.2 \pm 3.4	< 0.001
D-Dimer (μ g/L)	236.4 \pm 128.4	189.3 \pm 109.3	< 0.001	253.7 \pm 109.8	202 \pm 98.9	< 0.001
Fibrinogen (g/L)	3.9 \pm 0.9	4.2 \pm 1.1	> 0.05	4.1 \pm 1.1	4.25 \pm 1	> 0.05

WC- waist circumference, FPG- fasting plasma glucose, FPI- fasting plasma insulin, Total-C- total cholesterol, TG- triglyceride

both groups (from 49.6 ± 10.9 mg/dL to 55.5 ± 12.2 mg/dL with orlistat, and from 47.2 ± 9.3 mg/dL to 54.9 ± 8.6 mg/dL with sibutramine; $P < 0.001$ for both).

Both groups showed significantly reduced CRP levels after 6 months on the obesity program (from 6.1 ± 4.7 to 4.2 ± 2.7 mg/L with orlistat, and from 7.2 ± 4.8 to 4.9 ± 2.4 mg/L with sibutramine; $P < 0.001$ for both). D-dimer levels were also significantly lower (from 236.4 ± 128.4 to 189.3 ± 109.3 μ g/L with orlistat, and from 253.7 ± 109.8 to 202 ± 98.9 μ g/L with sibutramine; $P < 0.001$ for both).

Concerning liver function, AST and GGT levels decreased significantly during treatment in both groups ($P < 0.001$ for both), whereas there was no significant change in ALT. There was also no significant change in the serum fibrinogen values in either group. Serum homocysteine levels rose significantly from 10 ± 2.2 to 11.8 ± 3.7 μ mol/L in the orlistat group, and from 10.5 ± 3 to 12.2 ± 3.4 μ mol/L in the sibutramine group ($P < 0.001$ for both).

The adverse effects most frequently reported by patients receiving sibutramine were dry mouth ($n = 13$; 29.5%), constipation ($n = 15$; 34.1%), headache ($n = 6$; 13.6%), and insomnia ($n = 3$; 6.8%). Side effects reported by the orlistat group were gastrointestinal adverse effects such as flatulence, fatty stools and diarrhea ($n = 21$; 45.7%).

Discussion

Obesity is associated with significantly increased morbidity and mortality, and is now considered epidemic in most countries (11). Many obese individuals have problems such as impaired insulin sensitivity, abnormal blood lipid levels, hypertension, and high numbers of cardiovascular risk factors (12). Diet, exercise and lifestyle changes are still the main treatment recommendations for these patients. These steps are modestly effective in some cases, but for many patients they are ineffective. Drug treatment is often indicated, but is somewhat limited by the fact that only a small number of drugs that are well tolerated offer long-term efficacy in obesity management (9). Both orlistat and sibutramine are approved anti-obesity drugs. In line with findings from previous research, our results indicate that use of either of these agents in an obesity management program leads to significant weight loss (6-8). Both the drug groups in our study showed significant improvement in anthropometric and body composition parameters after a 6-month treatment period.

Earlier studies in obese patients have shown that both orlistat therapy and sibutramine therapy lead to significant improvements with respect to insulin sensitivity and serum lipid profile (13-16). The results of our study confirm that each of these agents, when combined with a low-calorie diet and exercise, reduce or eliminate lipid abnormalities and insulin resistance.

It is well established that obesity and, specifically, abdominal fat accumulation are important indicators of a proinflammatory state (17,18). Recent work has shown that serum CRP level is an independent risk factor for cardiovascular disease (19-21). Weight loss is an important step in reducing or eliminating several markers of inflammation, including CRP level (22-24). In our study, the orlistat and sibutramine treatment groups both achieved significant weight loss, and both also had significantly lower mean serum CRP levels after 6 months on the therapy program.

AST, ALT, and GGT are all sensitive indicators of hepatobiliary disorders, including fatty liver (25). Serum GGT activity is also associated with other pathological conditions, such as obesity and metabolic syndrome. Some studies have suggested that elevated serum GGT is associated with cardiovascular risk factors, mortality from cardiovascular disease, and mortality from all causes (26,27). Research has also revealed an independent association between serum GGT level and risk of developing type 2 diabetes mellitus in long-term follow-up (28). Other work has demonstrated improvement in the liver function of obese patients after weight reduction (29). Both sibutramine-induced weight loss and orlistat-induced weight loss lead to improvements in biochemical markers of fatty liver disease (30,31). Our data related to markers of fatty liver disease are further evidence that weight reduction through the use of these drugs added health benefits.

Elevated serum fibrinogen is pathophysiologically related to cardiovascular events and considered a major cardiovascular risk factor (32). One study revealed that a group of obese patients had significantly higher serum fibrinogen levels than a group of non-obese subjects (33). Results from studies that have examined the impact of weight loss on fibrinogen levels are conflicting; some have demonstrated an effect whereas others have not (34,35). Some authors have concluded that substantial weight loss (as opposed to more modest weight reduction) is needed in order to see a significant reduction in serum fibrinogen (36). Serum levels of fibrinogen are not influenced by the modest weight reduction achieved by using the two pharmacological agents in this study.

Obesity is a risk factor for thromboembolism. D-dimer is an end product of plasmin digestion of cross-linked fibrin and a direct marker of ongoing fibrinolysis (37). D-dimer is associated with future myocardial infarction risk and high concentrations have been observed in individuals with atherosclerosis (38,39). D-dimer has been associated with overall adiposity (40). To our knowledge, this is the first time that we observed statistically significant decreases in plasma D-dimer levels after significant weight loss achieved by both groups.

Elevated circulating homocysteine is known to be potentially modifiable risk factor for cardiovascular disease and death, and it appears to be largely independent of other conventional risk factors (41,42). Some studies have demonstrated that rapid weight loss following gastroplasty resulted in the elevation of plasma homocysteine concentrations, which would thus mitigate the beneficial cardiovascular effects of weight reduction (43,44). Some studies have also reported that plasma homocysteine concentrations increased following a weight reduction program in obese children and adolescents (45). One of the most intriguing observations of the present study is that weight reduction would lead to an increase in plasma homocysteine concentrations in obese women treated with orlistat and sibutramine in an obesity management program. A recent report indicated that folic acid supplementation decreased serum homocysteine concentrations in those women having higher baseline serum homocysteine concentrations before entering a weight reduction program (46,47). Thus, it is reasonable to institute adequate oral vitamin supplementation, especially folic acid supplementation, which might protect against increased homocysteine production during weight reduction. Further studies are warranted to establish this approach.

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