The Effects of Lifestyle Changes, Sibutramine and Orlistat in Obese Adults

Obez Hastalarda Yaşam Şekli Değişikliği Sibutramin ve Orlistat Tedavilerinin Etkileri

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ABSTRACT Objective: Obesity is a low-grade chronic inflammatory process and the main risk factor for accelerated atherosclerosis and cardiovascular events. There is growing interest in cardiovascular disease associated with obesity and metabolic syndrome, accordingly, pharmacotherapy to overcome the increasing incidence of obesity. We aimed to compare the metabolic effects of lifestyle changes, sibutramine and orlistat in obese adults after the 6-months of therapy in this study. **Material and Methods:** Forty-eight obese adults were randomized into three groups (n= 16 for each). Lifestyle changes (low caloric diet, behavioral changes, and exercise) were recommended for all of the groups. Additionally, group II and III took sibutramine (15 mg/day) and orlistat (3×120 mg/day), respectively. Pre- and post-treatment anthropometric measurements were performed; C-reactive protein (CRP), insulin resistance (HOMA-IR), and albuminuria levels were determined in the all of cases. **Results:** After the 6-month treatment, the mean weight loss was 5.3% in group I with lifestyle changes alone, 10.2% in group II (sibutramine group), and 8.4% in group III (orlistat group). In groups I, II, and III, body mass indexes ($p< 0.05$, $p< 0.001$, $p< 0.001$, respectively), waist circumferences ($p< 0.05$, $p< 0.001$, $p< 0.001$, respectively), and log-CRP ($p< 0.05$, $p< 0.01$, $p< 0.01$, respectively) decreased at the end of study. Furthermore, the HOMA-IR indexes decreased in the pharmacotherapy groups ($p< 0.05$ for both). Moreover, the reduction in log-albuminuria was significant ($p< 0.01$) in the sibutramine group, which had achieved the most weight loss. **Conclusion:** In obese adults, the use of pharmacotherapy in addition to lifestyle changes may effectively reduce cardiovascular risk factors such as inflammation and insulin resistance.

Key Words: Obesity; insulin resistance; albuminuria; sibutramine; orlistat; life style

ÖZET Amaç: Obezite, kronik inflamatuar bir süreç olup, hızlanmış ateroskleroz ve artmış kardiyovasküler olaylar için başlıca risk faktörüdür. Obezite ve metabolik sendrom ile ilişkili kardiyovasküler hastalıklar ve artan insidansının azaltılması açısından obezitenin tedavisine artan bir ilgi vardır. Bu çalışmada, yaşam tarzı değişikliği, sibutramin ve orlistat tedavilerinin obez hastalardaki, 6 ay sonrasındaki, metabolik etkilerinin değerlendirilmesi amaçlandı. **Gereç ve Yöntemler:** Çalışmaya alınan 48 obez yetişkin 3 gruba randomize edildi (her grupta, n=16). Her 3 gruba da yaşam şekli değişikliği (düşük kalorili diyet, davranış değişiklikleri, ve egzersiz) önerildi. Ek olarak, II. gruba 15 mg/gün sibutramin, III. gruba 3 × 120 mg/gün orlistat tedavileri uygulandı. Tüm hastaların, tedavi öncesi ve 6 aylık tedavi sonrası, antropometrik ölçümleri yapılıp, C-reaktif protein (CRP), insülin direnci (HOMA-IR) ve albuminüri düzeyleri belirlendi. **Bulgular:** 6 aylık tedavi sonrası, sadece yaşam şekli değişikliği önerilen grupta %5.3 (I. grup), sibutramin tedavi grubunda %10.2 (II. grup), orlistat tedavi grubunda ise %8.4 (III. grup) ağırlık kaybı saptandı. Her üç grupta da tedavi sonrası vücut kitle indeksi (sırasıyla; $p< 0.05$, $p< 0.001$, $p< 0.001$), bel çevresi (sırasıyla; $p< 0.05$, $p< 0.001$, $p< 0.001$) ve log CRP (sırasıyla; $p< 0.05$, $p< 0.01$, $p< 0.01$) düzeylerinde azalma saptandı. Ek olarak, farmakoterapi gruplarının HOMA-IR indekslerinde azalma (her ikisi için, $p< 0.05$) belirlendi. Ayrıca, ağırlık kaybının en belirgin olduğu sibutramin tedavi grubunda log albuminüri düzeyindeki azalma da anlamlı bulundu ($p< 0.01$). **Sonuç:** Obez bireylerde, yaşam şekli değişiklikleri ile birlikte bir farmakolojik ajanın kullanımı, obezitedeki inflamasyon ve insülin direnci gibi kardiyovasküler risk faktörlerini etkili şekilde azaltabilir.

Anahtar Kelimeler: Şişmanlık; insülin direnci; albüminüri; sibutramin; orlistat; yaşam biçimi

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Overweightness and obesity are the foremost public health problem in industrialized countries, and is rapidly increasing in developing countries. Obesity is defined as increased body fat mass, and excess adiposity is associated with systemic low-grade inflammation, which has been implicated in pathophysiology of various diseases. Obesity has reached epidemic proportions in both adults and children and is associated with numerous comorbidities, including insulin resistance, type II diabetes mellitus (DM), dyslipidemia, arterial hypertension, and major cardiovascular diseases (CVDs).[1-3] Insulin resistance and the development of atherosclerosis due to obesity have been associated with inflammation.[2] C-reactive protein (CRP), which reflects inflammatory state and microalbuminuria are positively correlated with cardiovascular morbidity and mortality.[4-7]

Obesity is a multifaceted disease which requires multiple approaches to successfully overcome its increase. Lifestyle changes (low caloric diet, behavioral changes, and exercise) in obese adults are usually unsuccessful for weight loss and maintaining any achieved weight loss. Thus, pharmacological agents may help to encourage weight loss and to increase compliance with weight loss programs.[8] Two agents, sibutramine and orlistat are currently approved for long-term management of obesity. It is convenient to evaluate these drugs for their effects on body weight and cardiometabolic risk factors. Sibutramine and orlistat are efficient in weight loss and in maintaining the achieved weight loss.[8] Sibutramine and its metabolites inhibit the re-uptake of serotonin, norepinephrine, and dopamine.[9,10] It causes weight loss via its anorectic effect and through stimulation of thermogenesis.[9,10] In contrast, orlistat reduces intestinal fat absorption by inhibiting pancreatic and gastric lipase enzymes.[11] Sibutramine and orlistat treatments have been proven superior to placebo in providing weight loss.[10,12,13]

The aim of the present study was to investigate the effects of lifestyle changes, and accompanying sibutramine or orlistat treatments on anthropometric measurements, CRP, insulin resistance, albuminuria levels and other routine laboratory tests in obese adults.

MATERIAL AND METHODS

PATIENT SELECTION

The study involved 48 patients who had applied to the Endocrinology and Metabolic Diseases outpatient clinic with the complaint of obesity. The body mass indexes (BMIs) of the patients were >30 kg/m², and all were willing to lose weight. The study was approved by the institutional ethics committee. The written informed consent of each participant was also obtained. This was a prospective, randomized, unblinded, open-label, clinical study. The histories of all the patients were recorded, and physical examinations were performed before and after the 6-month treatment. Height, weight, waist circumference (WC), and hip circumference (HC) were also measured, and body mass index (BMI) was calculated based on the formula of BMI= weight (kg)/height (m)². Microalbuminuria was defined as in the range of 30-299 mg per 24 h.

Patients with therapy-resistant hypertension, CVD, chronic liver disease, chronic renal failure, neurological and/or psychiatric diseases, history of treatment for weight loss, patients with taking lipid lowering drugs, and pregnant patients, breastfeeding mothers, as well as patients over 65 years of age or under 18 years of age, were excluded from the study.

LIFESTYLE CHANGES AND PHARMACOTHERAPY

Obese adults were subsequently allocated into one of the three groups. Any pharmaceutical company was not involved in the study (n= 16 for each). Group I, the control group, [12 female and 4 male; median age: 37(32-44) years]was recommended only lifestyle changes. Group II [12 female, 4 male; median age: 34 (23-43) 35.5 ± 11.4 years] received sibutramine (15 mg/day) and Group III [13 female, 3 male; median age: 39 (31-46) 38.3 ± 8.9 years] received orlistat (3 × 120 mg/day), in addition to recommendations of lifestyle changes.

All of the patients in the three groups were recommended a low caloric diet that would pro-

vide a 500 kcal/day energy deficit. The patients were trained on compliance with the diet. To avoid monotony in the diet, diet change lists were provided. The diet was composed of 50% carbohydrate, 30% fat, and 20% protein and the recommended daily dietary fiber intake was 14 g/1000 kcal. The patients were also recommended 45-60 minute brisk walks at least 3 days a week, in addition to behavioral changes. They were followed-up at 15-day intervals for compliance to lifestyle changes and for use of the drugs and any complaints associated with the drug use.

LABORATORY ANALYSES

After the patients had fasted for 8-12 hours, blood and urine samples were collected between 08^{00} and 09^{00} hours in the morning. On the same day, complete blood cell counts, liver and renal function tests, lipid profiles, and insulin levels were determined. The insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) mathematical formula [HOMA-Ir= fasting insulin (μu/ml) × fasting glucose (mmol/L) /22.5]. Serum CRP (Schiapparelli Biosystems, Netherlands) and urine albumin (Olympus Life and Material Science Europa GmbH, Germany) levels were determined on the same day by immunoturbidimetric methods.

Statistical analysis

The SPSS 12.00 computer package program was used for all statistical analyses. Data were presented as median (interquartile range), unless indicated otherwise. The normal distribution of the variables was evaluated with the Kolmogorov-Smirnov test, and logarithmic transformations were performed to normalize data with skewed distribution (CRP and albuminuria). The possible differences between the baseline values of the groups were analyzed with *Kruskal-Wallis* and *Mann-Whitney U*-tests, and the differences between the repeated measurements were studied with *Wilcoxon signed-rank* test. Possible correlations between nonparametric data were evaluated with *Spearman's rho* test. $p< 0.05$ was considered statistically significant, while multiple comparisons were corrected Bonferroni method.

RESULTS

Forty eight obese adults (37 female, 11 male; mean age: 37.2±9.8 years) comprised the study population. There were 7 patients with hypertension (3 in group I, 1 in group II, and 3 in group III) and 5 patients with DM (2 in group I, 2 in group II, and 1 in group III). Antihypertensive and antidiabetic drugs taking by the patients were not changed during the study period. The baseline HOMA-IR index was correlated with systolic blood pressure (SBP) and WC ($r= 0.381$, $p= 0.012$ and $r= 0.462$, $p= 0.002$, respectively). The log albuminuria level was correlated with high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels ($r= -0.371$, $p= 0.028$ and $r= 0.506$, $p= 0.001$, respectively). The log CRP level was correlated with fasting blood glucose (FBG) and WC ($r= 0.451$, $p= 0.004$ and $r= 0.358$, $p= 0.023$, respectively) and FBG was correlated with BMI ($r= 0.420$, $p= 0.005$). The anthropometric, clinical, and laboratory findings of the three groups at baseline and at 6-month after the treatment are presented in the Table 1. No differences were determined between the baseline values of the three groups ($p> 0.05$ for all).

In the control group, that only lifestyle changes was recommended, the mean weight loss was 3.5 (2.0-8.6) after 6 months of the treatment, compared to the baseline ($p= 0.011$). The reductions in BMI, WC, HC, postprandial blood glucose (PPBG), total cholesterol (TC), and log CRP levels were significant in this group, in addition to the weight loss (Table 1). Two patients in this group were excluded from the study because of their non-compliance with the study protocol.

In the 6-month sibutramine treated group, the mean weight loss was 11.0 (9.0-13.0) kg (compared to the baseline ($p< 0.001$). In this group, BMI, WC, HC, FBG, PPBG, insulin, HOMA-IR, LDL-C, TG, log CRP, and log albuminuria levels were significantly decreased (Table 1). One patient with internal hemorrhoid aggravation in this group was dropped from the study.

In the 6-month orlistat treated group, the mean weight loss was 7.5 (4.7-8.5) kg compared to the baseline ($p< 0.001$). In this group, BMI, WC,

TABLE 1: Anthropometric, clinical, and laboratory findings of the study groups before the treatment and after a 6-month treatment.

	Lifestyle changes alone		Lifestyle changes + pharmacotherapy			
			Sibutramine		Orlistat	
	Baseline	After 6-month	Baseline	After 6-month	Baseline	After 6-month
Weight (kg)	94(91-106)	90(85-101)*	98(87-106)	85(82-103)***	94(87-106)	86(77-99)**
BMI (kg/m²)	38(36-42)	35(33-40)9*	38(31-42)	33(27-37)***	36(33-45)	32(29-38)***
WC (cm)	109(102-119)	104(100-114)*	106(100-110)	99(92-103)***	103(100-115)	98(93-112)***
HC (cm)	114(111-123)	111(107-116)*	119(109-128)	113.7±11.9***	115(108-128)	109(100-125)***
SBP (mmHg)	120(105-152)	120(107-137)	125(110-140)	120(110-130)	137(120-142)	120(110-140)*
DBP (mmHg)	80(67-82)	75(65-82)	80(70-85)	75(70-80)	87(77-96)	80(70-90)
FBG (mg/dl)	102(90-127)	102(88-13)	102(90-121)	100(89-112)*	96(86-125)	87(80-107)***
PPBG (mg/dl)	125(108-154)	122(103-145)*	126(101-148)	115(100-138)*	127(111-148)	114(96-125)***
Insulin (IU/ml)	14(10-24)	14(7-20)	13(10-23)	11(8-21)***	15(11-18)	11(8-14)*
HOMA-IR	4.1(2.3-7.9)	3.6(2.1-5.4)	4.0(2.5-5.7)	2.8(2.2-4.8)*	2.7(1.4-4.9)	2.1(1.3-3.3)*
TC (mg/dl)	215(184-243)	197(172-232)*	204(185-244)	198(184-211)	204(176-231)	197(154-223)
HDL-C (mg/dl)	42(37-48)	43(37-47)	43(41-47)	42(41-48)	43(35-47)	41(36-53)
LDL-C (mg/dl)	157(117-170)	129(107-37)	142(131-170)	136(118-153)*	153(116-164)	121(95-153)*
TG (mg/dl)	146(117-216)	129(117-194)	186(135-255)	168(111-224)*	196(138-215)	152(122-188)
CRP (mg/l)×	10(8-15)	8(5-13)*	8(6-13)	3.5(3-6)**	14(9-21)	12(5-15)**
Albuminuria (mg/dl)×	17(9-29)	13(8-22)	22(18-122)	12(8-76)**	21(13-24)	15(12-18)

BMI: body mass index, WC: waist circumference, HC: hip circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, PPBG: postprandial blood glucose, HOMA-IR: Homeostasis model assessment of insulin resistance, TC: total cholesterol, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, TG: Triglyceride CRP: C-reactive protein.

×Logarithmic transformations were applied before statistical analysis × Compared to baseline values, *p<0.05, **p<0.001, ***p<0.001.

HC, SBP, FBG, PPBG, insulin, HOMA-IR, LDL-C, and log CRP levels were significantly decreased, in addition to the weight loss (Table 1). One patient with dyspeptic complaints in this group was dropped from the study.

When compared with the control group, the reductions in the weight, BMI, WC, log CRP and log albuminuria in the sibutramine group, and the reduction in FBG in the orlistat group were significant (p= 0.016, p= 0.031, p= 0.047, p= 0.021, p= 0.005 and p= 0.046, respectively). In the control group, the changes in the BMI and CRP values were correlated (r= 0.689, p= 0.009, Table 2), and the change of the HOMA-IR index was correlated with the baseline HOMA-IR index (r= 0.645, p= 0.013). The change in CRP values was correlated with the baseline CRP levels in the sibutramine group, (r= 0.918, p< 0.001), and it was correlated with the change in the HOMA-IR index in the orlistat group (r= 0.663, p= 0.010). In the sibutramine and orlistat groups, the changes in urine albumin levels were only correlated with baseline urine albumin levels (r= 0.948, p< 0.001 and r= 0.969, p< 0.001, respectively).

DISCUSSION

This is a small randomized unblinded study to compare the metabolic effects of lifestyle changes, sibutramine and orlistat in obese adults with 6 months of therapy. In this study, the CRP level and HOMA-IR index were correlated with WC in obese adults. In addition, there were reductions in the levels of inflammation (CRP), insulin resistance (insulin, HOMA-IR index), and other markers of atherosclerosis (WC, LDL-C, albuminuria) associated with weight loss. In the pharmacotherapy groups, where the weight loss was more marked, these improvements were more prominent than were those in the control group.

The overall prevalence of overweight is 25.0% and of obesity is 19.4%, in our country.[14] It is estimated that 1.1 billion adults in the world are overweight and that 312 million of them are obese. Thus, the increasing incidence of obesity is consid-

TABLE 2: Correlations in the study

Correlations	r	P
Baseline values of all patients		
HOMA-IR-SBP	0.381	0.012
HOMA-IR-WC	0.462	0.002
Albuminuria-HDL-C	0.371	0.028
Albuminuria-TG	0.506	<0.001
CRP-FBG	0.451	0.004
CRP-WC	0.358	0.023
FBG-BMI	0.420	0.005
Lifestyle changes alone		
ΔCRP-ΔBMI	0.689	0.009
ΔHOMA-IR-baseline HOMA-IR	0.645	0.013
Lifestyle changes + sibutramine		
ΔCRP-baseline CRP	0.918	<0.001
Δalbuminuria-baseline albuminuria	0.948	0.001
Lifestyle changes + orlistat		
ΔCRP-ΔHOMA-IR	0.663	0.010
Δalbuminuria-baseline albuminuria	0.969	<0.001

HOMA-IR: Homeostasis model assessment of insulin resistance, SBP: systolic blood pressure, WC: waist circumference, HDL-C: high-density lipoprotein cholesterol, TG: Triglyceride FBG: fasting blood glucose, BMI: body mass index CRP: C-reactive protein. Δ: difference between the pre- and post-treatment values.

ered to be a public health problem.[15] Obesity leads to CVD and increased mortality due to CVD and all other reasons.[16,17] The relative risk of mortality due to CVD in obese women has been reported to be 4.1 in a 16-year follow-up.[17] Moreover, a 3.3 fold increase in CVD mortality and two fold increase in mortality due to all other causes have been demonstrated in obese men over a 26-year follow-up.[16]

Obesity is an independent risk factor for CVD.[3] On the other hand, insulin resistance, DM, and dyslipidemia (high TG and/or low HDL-C), known as the classical risk factors for CVD, are more common in visceral obesity. These conditions accompanying visceral obesity significantly increase the risk of CVD.[3] In our study, WC, a marker of visceral obesity, was found positively correlated with CRP and HOMA-IR index.

The association between insulin resistance and visceral obesity is well known.[3] Increased expression of free fatty acids (FFA) and tumor necrosis factor-alpha (TNF-alpha) from the adipose tissue leads to development of insulin resistance[14]; however, in insulin resistance, lipoprotein lipase activity is affected. Thus, the levels of FFA increase, leading to a vicious cycle. In our obesity cohort, WC was correlated with insulin resistance. Considering these facts, it is obvious that the accompanying dysmetabolic conditions should also be overcome in addition to weight loss, which is the primary aim. After a 12-week treatment with sibutramine[15] and orlistat,[16] a significant reduction was observed in HOMA-IR index, in addition to weight loss. In our study, the HOMA-IR indexes and LDL-C levels were significantly reduced in the pharmacotherapy groups in which a higher rate of weight loss was achieved.

C-reactive protein, a sensitive marker of systemic inflammation, is a potent predictor of cardiovascular events independent of other classical risk factors.[17] CRP increases the expression of nitric oxide synthetase,[18] chemokines, and adhesion molecules[19] from the endothelial cells. In addition to direct effects, the inflammatory nature of obesity leads to endothelial dysfunction indirectly by its contributions to development of insulin resistance.[1] TNF-alpha is known to cause insulin resistance[20] and inflammatory markers such as CRP have been associated with insulin resistance in obese individuals.[21] In our study, CRP level was correlated with FBG and WC, and significant decreases were determined in the levels of CRP in all of the groups, in addition to weight loss. Reduction in the CRP level was correlated with the change of the BMI in the control group that was recommended only lifestyle changes, and with the change of the HOMA-IR index in the orlistat group.

Microalbuminuria has been reported to be a prognostic marker of CVD in both diabetics and non-diabetics[22] and the positive effects of regression of albuminuria on cardiovascular events have been reported in diabetics.[23] Previous studies have demonstrated a relationship between obesity and microalbuminuria,[24] and reductions in albuminuria levels and microalbuminuria frequency in obese individuals who experience weight loss after gastric surgery.[25] In our study, urine albumin levels were correlated negatively with HDL-C level, and positively with TG level in obese adults. The reduction

in the albuminuria level was significant in the sibutramine group, in which significant weight loss was achieved.

The correlation between microalbuminuria and obesity indexes has been reported to be independent of blood pressure, blood glucose, and renal functions.[24] On the contrary, some studies have shown that the microalbuminuria levels of obese individuals without diabetes and/or hypertension are not different from non-obese individuals.[26] Reductions in albuminuria levels are not significant after weight loss in obese adults without other components of metabolic syndrome, while they are significant in obese adults with other components of metabolic syndrome.[25] Similarly, increased albuminuria levels in obesity are related to increased risks of CVD and mortality, but are independent of obesity indexes.[7] These data suggest that albuminuria in obesity may not be directly associated with obesity but rather is associated with accompanying dysmetabolic conditions. In our study, albuminuria correlated with only dyslipidemia. Moreover, a reduction in the level of albuminuria occurred in the sibutramine group, in addition to weight loss. However, this reduction only correlated with baseline albuminuria levels.

This study has some limitations. The small sample sizes are the main limitation of the study. A better design could have been blinded and placebo controlled with the groups assigned to receive lifestyle changes plus placebo, lifestyle changes plus sibutramine and lifestyle changes plus orlistat. The amount of lifestyle changes may be variable among different subjects. Though a minimum duration of walking, and dietary composition was recommended to the subjects in all the treatment arms, some subjects may have been involved in greater exertion than others and this may have influenced some results. It would be better to examine urine albumin creatinine ratio than urine albumin as a measure of albuminuria.

The obvious improvements may be obtained by the pharmacotherapy on the markers of metabolic risk factors in addition to weight loss, although weight loss in obese adults may also be achieved by only lifestyle changes. In conclusion pharmacotherapy should be considered when the expected weight loss cannot be achieved and/or when reductions in cardiovascular risk markers, such as inflammation and insulin resistance, can not be achieved by non-pharmacological approaches.

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