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Original Research Article

The clinical efficacy of orlistat in the treatment of obesity

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ABSTRACT

Background: The prevalence of obesity is gradually increasing worldwide and reaches an epidemic extent. Currently, treatment of obesity with pharmacological options has gained importance due to the frequent failure of lifestyle changes. Anti-obesity medications have an unfortunate history that make many clinicians uncomfortable with their prescription. In this study, we aimed to examine the effect of orlistat on weight loss and glycaemic parameters.

Methods: Forty patients under orlistat treatment between November 2017 to October 2018 were recruited and their weight, body mass index (BMI), glucose, insulin, and the homeostatic model assessment of insulin resistance (HOMA-IR) values were recorded before and after treatment. Patients aged >18 years with BMI≥40 kg/m² were enrolled to the study while having the diagnosis of diabetes mellitus, those with gastrointestinal diseases, who were pregnant or in lactation period, using drugs that have an effect on weight, and who did not come their follow-up after 12 weeks were excluded.

Results: Thirty-four patients were female, 6 were male, and the mean age was 42.75 ± 10.60 years. The mean height found as 161.10 ± 8.98 cm. Before treatment, the mean weight was 120.62 ± 16.56 kg, BMI was 46.43 ± 4.61 kg/m², and HOMA-IR was 5.84 ± 3.58 . After 12 weeks, it was observed that the mean weight decreased to 112.67 ± 16.21 kg, BMI to 43.35 ± 4.55 kg/m², and HOMA-IR to 3.73 ± 2.38 . There was a statistically significant difference in these parameters compared to the pre-treatment values.

Conclusions: Given the lack of non-surgical treatments, or listat can provide significant benefits in the current clinical practice when combined with the appropriate diet.

Keywords: Insulin resistance, Pharmacotherapy, Obesity, Orlistat, Weight loss

INTRODUCTION

Obesity is caused by the deterioration of the body's energy balance in favor of the energy that received from the energy that consumed. Although the exact cause of the disease is not known, it is a complex clinical condition in which many factors like biological, psychosocial, and behavioral are involved. It predisposes to various diseases such as diabetes mellitus (DM), hypertension, ischemic heart disease, cerebrovascular disease, gallstones, functional respiratory disorders, polycystic ovary syndrome, non-alcoholic fatty liver disease, and cancer.^{1,2}

The frequency of the obesity has gradually increased in our country as in all over the world and has reached the extent of epidemic. Worldwide, a total of 712 million people, including approximately 108 million children and 604 million adults, were reported to be obese in 2015, also the prevalence has been reported to double in 70 countries.³ In another study conducted between 1980 and 2013, which includes also overweight people, it was found that this number reached 2.1 billion. In the same study, it was shown that the prevalence increased by 27.5% in adults and 47.1% in children.⁴ Prevalence studies conducted in our country have also shown us that obesity is a serious public health problem in parallel with

other studies in the world. In 'the Turkish diabetes epidemiology study' (TURDEP-I), when the frequency of obesity was evaluated as a subgroup, this rate was found to be 22.3%. In the TURDEP-II study, where the same centers were selected 12 years later, it was reported that the prevalence increased by 34% in women and 107% in men and increased to 31.2% compared to the previous study. In the light of all these data, it is easy to be understood why the World Health Organization (WHO) considers obesity as one of the 10 most risky diseases.

Nowadays, pharmacological treatment of obesity has gained importance because diet and lifestyle changes are mostly unsuccessful. However, antiobesity drugs have an unfortunate history that has left many clinicians uncomfortable with their use. Especially experience with fenfluramine, the agent was deprecated in the United States in 1997 due to causation valvular heart disease and pulmonary hypertension. In addition, drugs such as amphetamine, dinitrophenol, and aminorex are no longer used with respect to the different side effects. Therefore, the use of antiobesity drugs was suspended for a period.

Orlistat, one of the limited number of obesity drugs in our country, is a gastric and pancreatic lipase inhibitor and it performs this reaction irreversibly. Orlistat which known as tetrahydrolipstatin, is a synthesized derivative of lipstatin produced by *Streptomyces toxytricini* (a gram positive bacteria belonging to the genus *streptomyces*). The drug with chemical formula C₂₉H₅₃NO₅ is a diastereomeric molecule with four chiral centers and a molecular weight of 495.7. Orlistat reduces intestinal fat absorption by 30% via binding to the serine residues of gastric and pancreatic lipases in the gastrointestinal lumen by covalent bonds. It has been reported to affect lipases but not inhibit other pancreatic enzymes such as phospholipase A2, amylase or trypsin. 9

In this study, we aimed to investigate the effect of orlistat treatment on weight loss and glycemic parameters as a contribution to the limited number of studies conducted in our country.

METHODS

Study population

This retrospective study involving participants was performed in line with the principles of the declaration of Helsinki and approved by Bakirkoy Dr. Sadi Konuk Training and Research Hospital (Istanbul, Turkey) Ethics Committee with reference number: 2020/353. Forty patients who admitted to outpatient clinics of Kanuni Sultan Suleyman Training and Research Hospital (Istanbul, Turkey) endocrinology and metabolism diseases department between November 2017 and October 2018 and were under orlistat treatment for obesity were included in this study. Patients over eighteen years of age with a body mass index (BMI) ≥40 kg/m² were enrolled whilst pregnant or breastfeeding women, patients with a diagnosis of DM, gastrointestinal

disease such as cholestasis or chronic malabsorption syndrome, using another drug that has an effect on weight, and those who did not come to follow-up 3 months later were excluded from the study.

Height, weight and BMI of all patients were recorded before starting therapy. Then, the weight of the patients at the 4th and 12th weeks of the therapy was measured again and their BMIs were calculated. In addition, glucose, insulin and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) levels of the patients at the beginning and after 12 weeks were obtained from the hospital database system. All data were recorded in preprepared forms. BMI was calculated by dividing the weight of the patients in kilograms by the square of their height in meters (kg/m²). For HOMA-IR, fasting blood glucose level (mg/dL)×fasting insulin level (uIU/mL)/405 formula was used.

Statistical method

All statistical analysis in the study were performed in computer software SPSS version 22.0 (SPSS Inc., Chicago IL) program. Descriptive statistics were expressed as mean \pm standard deviation (SD) and median (minimum-maximum), and categorical variables as frequency (percentage). The distribution of data was analyzed by using the Shapiro Wilk test. Friedman test was used to analyse 3 dependent variables that do not have normal distribution. Post-hoc comparisons of variables that were found to be statistically significant at the end of the test was made by using the Bonferroni test. Two dependent variables were compared with Paired t test when the normal distribution condition was provided and Wilcoxon test was used when the normal distribution condition was not met. P≤0.05 was considered as statistically significant.

RESULTS

The data of 147 patients in whom under orlistat therapy were retrospectively analyzed and 107 patients who did not meet the criteria were excluded from the study. Out of 40 patients, 34 (85%) were female, 6 (15%) were male, and the mean age was 42.75±10.60 (23-69) years. Twenty two (55%) of the patients had no other concomitant disease, whilst 12 (30%) had hypothyroidism, and 6 (15%) had hypertension. The mean height was found to be 161.10±8.98 cm. The mean levels of weight and BMI before, at the 4th, and at the 12th week of the therapy are shown in Table 1. The mean decrease in weight and BMI of the patients after four weeks was 4.05 ± 2.03 kg and 1.56 ± 1.11 kg/m², respectively, and these parameters changed to 7.95±3.18 kg and 3.08±1.25 kg/m² after 12 weeks. The mean glucose values before starting therapy was 99.06±14.31 mg/dl and was 91.48±9.99 mg/dl at 12th week. The mean insulin levels of the patients was 148.33±96.79 uIU/ml at the beginning of therapy, while it was observed that this decreased to 51.53±29.26 uIU/ml after 12 weeks. The mean HOMA-

IR level initiation of the therapy was 5.84±3.58 and after

the 12^{th} week it was 3.73 ± 2.38 .

Table 1: The mean levels of weight and BMI before, at the 4th and 12th week of the therapy.

Variables	Weight (kg)	BMI (kg/m²)
Before starting treatment	120.62±16.56	46.43±4.61
4 weeks later	116.57±16.21	44.87±4.58
12 weeks later	112.67±16.21	43.35±4.55

Table 2: The change in weight and BMI values before, 4th and 12th week after therapy.

Variables	Initiation ^a	4 th week ^b	12 th week ^c	P value	Post-hoc p value
Weight (kg)	117 (97-179)	113 (93-175)	110 (90-168)	<0.001	a-b: <0.001 a-c: <0.001 b-c: <0.001
BMI (kg/m²)	46.29 (38.77-59.23)	44.70 (37.26-58.01)	43.42 (35.38-56.80)	< 0.001	a-b: <0.001 a-c: <0.001 b-c: <0.001

Table 3: Evaluation of the change in weight loss, glucose, insulin, and HOMA-IR levels before starting and at the 12th week of the therapy.

Variables	Initiation	12 th week	P value
Weight loss (kg)	4.05±2.03	7.95±3.18	< 0.001
Glucose (mg/dl)	94 (80-141)	90 (76-121)	0.005
Insulin (uIU/ml)	21.00 (7-75.40)	13.10 (6.50-54.90)	< 0.001
HOMA-IR	5.31 (1.55-20.14)	3.00 (1.28-13.54)	< 0.001

Change of weight and BMI due to the outset and other time periods is presented in Table 2. Significant difference was determined in these parameters before starting therapy and at the 4th and 12th weeks (p<0.001). According to the post-hoc analysis, for both weight and BMI, initiation-4th week, initiation-12th week, and 4th-12th week changes were shown a statistically significant difference. There was a significant decrease in the initial weight and BMI levels at the end of the 4th and the 12th weeks as well as in the 12th week compared to the 4th week.

The results of the analysis performed to examine the change in weight loss, glucose, insulin and HOMA-IR levels before starting and at the 12th week of the therapy are summarized in Table 3. The weight loss of the patients at the end of the 12th week was significantly higher than before the therapy was started (p<0.001). Significant difference was also noted with respect to glucose, insulin and HOMA-IR levels at the end of the 12th week compared to the beginning of the treatment (p=0.005, p<0.001, p<0.001 respectively).

DISCUSSION

Being successful against obesity will have medical, social and economic benefits which will lead to improvement in the health quality of populations, increase in life expectancy, and reduction in health services costs. Therefore, it is an important health problem that requires close monitoring and effective treatment. Most

algorithms recommended drug therapy as the next step for people who cannot achieve their weight loss goal despite diet and exercise. Pharmacological treatment is recommended for patients with BMI≥30 kg/m² or for patients with BMI between 27-29.9 kg/m² and having at least one of the comorbid diseases such as hypertension, dyslipidemia, and type 2 DM.^{1,10} In any case, only medication or only surgical treatment is not suitable without lifestyle changes. The complex pathogenesis of obesity has left clinicians despair for treatment.

Nowadays, there is no drug that provides ideal conditions for obesity treatment. Widely used drugs in the treatment of obesity in the world are phentermine, phentermine/topiramate, lorcaserin, naltrexone/ bupropion, diethylpropion, liraglutide, and orlistat. 1,2,10 In our country, just orlistat and liraglutide are used for obesity treatment. Orlistat was approved by the US Food and Drug Administration (FDA) in 1999 for long-term use.

In the previous study, it was found that patients using orlistat lost an average weight of 4.05 ± 2.03 kg after 4 and 7.95 ± 3.18 kg after 12 weeks. The effectiveness of Orlistat treatment has generally evaluated on a short- or long-term basis and weight loss has evaluated in kg or percentage. Few studies in the literature have chosen four weeks on a short-term basis. In one of these studies, Trouillot et al, have compared 23 obese patients who used 120 mg orlistat 3 times a day in addition to a diet of 1200-1500 kcal/day with a BMI of 30-41 kg/m² and a placebo group. Similar to this study, the patients in the orlistat therapy group lost 3.8 kg at the end of 4 weeks. Different

results were obtained in studies in which the effectiveness of the drug on weight loss was evaluated over kg and the observation period was taken for 12 weeks. These diversities may be due to the difference in the diet applied and the daily calorie amount selected in the diet, or various factors such as the selected patient group or the dose of the drug used. Drent et al, have studied the effect of orlistat therapy on weight loss by giving 500 kcal/day diet to obese patients for four weeks. In a total of 39 patients for whom all data were available, including 20 patients (BMI:30.6±3.7 kg/m²) on orlistat and 19 patients (BMI:30.0±3.7 kg/m²) in the placebo group, weight loss after 12 weeks was 4.3 ± 3.4 kg and 2.1 ± 2.8 kg. respectively. 12 In another study involving hypertensive patients aged 18 to 75 years with a BMI above 25 kg/m², weight loss was detected as 3.7 kg in the treatment group (calorie restricted diet and orlistat 360 mg/day) and 2.0 kg in the placebo group (calorie restricted diet only). 13 Compared to the studies mentioned above, weight loss results after 12 weeks seem to be higher in this study. However, in the XENDOS (XENical in the prevention of diabetes in obese subjects) study, which is one of the most important studies on this subject, 3305 patients between the ages of 30-60 years with BMI≥30 kg/m² were included and weight loss at the end of 1 year in the treatment group was found to be significantly higher than the placebo group (10.6 vs 6.2 kg; p<0.001). When the study was examined in detail, it was also seen that the short-term weight loss was higher in the treatment group alike to our findings.14 In a study conducted by Ozkan et al, which consisted of 30 patients, there was a reduction of 8.42% (p<0.001) in body weight and 8.39% (p<0.01) in BMI with three months of orlistat with diet therapy. While the initial weight of the patients was 95.01±17.89 kg, it decreased to 87.72±16.67 kg at the end of the third month, and weight loss was observed at a similar rate in our study. 15 In another study conducted in our country, Kaya et al compared 4 treatment groups and reported a decrease of $3.64\pm0.97~kg/m^2$ in BMI of the group using orlistat at the end of 12th week. 16 This result also supports the 3.08±1.25 kg/m² reduction in BMI in this study.

It should not be ignored that voluntarily weight loss is associated with a significant correction of risk factors. Pagotto et al reported that losing 10 kg of weight caused a decreasement of blood pressure 10 mmHg, fasting blood glucose by 50%, total cholesterol level by 10%, low density lipoprotein cholesterol level by 15%, triglyceride level by 30% and also an increasement of high density lipoprotein cholesterol level by 8%.¹⁷ The process that starts with insulin resistance in obesity can progress to type 2 DM occurrence. Although some studies reported that insulin resistance was not always observed, the general view is that weight loss is associated with improvement in glycemic parameters and a decrease in cardiovascular disease risk factors. In a large-scale study called diabetes prevention program (DPP), 3234 patients with BMI: 34.0±6.7 kg/m² are divided into three groups which are placebo (n:1082),

metformin 850 mg twice daily (n:1073), and lifestyle change (n:1079). In the group with lifestyle changes and resulting weight loss of 7%, a reduced risk of occuring new diabetes was reported as 58% (31% in the metformin group). 18 In the Finnish diabetes prevention study, the incidence of diabetes in the weight loss with exercise group has decreased compared to the control group. 19 In addition to studies on the effects of weight loss, various studies have reported that with orlistat therapy fasting blood glucose, insulin and insulin resistance has decreased in obese patients without diabetes, and haemoglobin A1c value in diabetic patients. 20,21 In the XENDOS trial, the cumulative incidence of diabetes after 4 years of therapy was 9% in the placebo group and 6.2% in the orlistat group, concluding a 37.3% risk reduction in the group receiving orlistat.¹⁴ Similar to the literature, in our study, a significant decrease was found in the fasting blood glucose, insulin and insulin resistance of nondiabetic patients.

Some limitations should be considered in this study. The first is that the study was retrospective. Second, the relatively small sample size had been made it less likely to draw comprehensive causal results. Finally, the study does not include long-term data on the effects of the drug on obesity-related morbidity and mortality, particularly on cardiovascular disease.

CONCLUSION

In conclusion, given the lack of non-surgical therapies, orlistat can provide significant benefits in this clinical practice when combined with the appropriate diet.

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