Lipase inhibitor orlistat: An old but still effective weapon

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Abstract

Nowadays, the pharmacological treatment of obesity has increased its significance due to the failure of conventional obesity treatments. Thus, Orlistat which is a lipase inhibitor is being used as an anti-obesity medication in many countries. In this study, the effect of Orlistat on weight loss and metabolic parameters in Turkish female patients was evaluated. Female patients with diagnosis of obesity who were followed up in Kutahya Training and Research Hospital were evaluated via retrospective observation. A total of 100 patients with body mass index (BMI-kg/m²) of >40, who were regularly followed up every month and compliant with their treatment (diet, exercise and orlistat) were included in the study. Monthly values of weight loss and BMI, along with baseline - 12th week values of fasting blood glucose, insulin, glycated hemoglobin (HBA1c), lipid profile, creatinine, aspartate aminotransferase, alanine aminotransferase and thyroid-stimulating hormone of patients who received orlistat 120 mg three times a day for 12 weeks in addition to diet and exercise were evaluated. Mean weight loss values of the patients using orlistat in the 1st, 2nd and 3rd month were found as 3.6 ± 0.5 kg, -2.2 ± 0.1 kg and -1.8 kg, respectively (p <0.0001). The median BMI values at baseline, in 1st, 2nd and 3rd months were 43.1 kg/m² (40.0-47.0), 41.7 kg/m² (39.0-45.4), 40.5 kg/m² (38.2-44.9), and 39.8 kg/m² (37.2-44.2), respectively (p <0.0001). Significant decreases in glycemic parameters including fasting blood glucose, HBA1c, and fasting insulin levels were provided (all, p <0.0001). Furthermore, positive effects were found on all lipid profiles except HDL cholesterol (p <0.05). Even in an early period of 12 weeks, Orlistat treatment was observed to significantly reduce BMI, insulin, HBA1c, total cholesterol, high-density lipoprotein and triglyceride values of Turkish female patients. Orlistat usage with diet and exercise can be beneficial for reducing the risk of glucose intolerance and cardiovascular disease.

Keywords: Orlistat, obesity, effectiveness, safety

Introduction

Obesity is defined as the excessive and abnormal accumulation of body fat in a way that disrupts health. Obesity plays a central role in the development of several risk factors and chronic diseases such as hypertension, dyslipidemia, and type 2 diabetes mellitus, that induce cardiovascular morbidity and mortality. It ranks second after smoking among the preventable causes of death.

It is a chronic disease that needs to be treated due to its effects on quality of life and the medical problems it causes. Therefore, weight control is especially significant in reducing morbidity and mortality [1]. Although various obesity indices such as body weight, waist circumference and body fat measurement have been suggested, body mass index (BMI), is widely used as an index for the diagnosis and treatment of obesity [2].

Lifestyle treatments to improve diet and physical activity are considered as the first-line treatment of obesity. However, if these fail, anti-obesity medications are recommended as adjunctive therapy. Current anti-obesity drugs are recommended for adults with a BMI of 30 kg / m² or BMI of 27 kg / m² with at least one comorbid disorder such as diabetes mellitus (DM), hypertension, hyperlipidemia, or sleep apnea [3]. Currently, phentermine, orlistat, phentermine/topiramate extended-release, lorcaserin, naltrexone sustained-release / bupropion and liraglutide are the anti-obesity drugs approved by the US Food and Drug Administration (FDA). Drugs except for orlistat which reduce fat absorption, act by reducing appetite and increasing the feeling of satiety through the central nervous system [4].

Orlistat acts by inhibiting pancreatic and gastric lipases. Triglycerides (TG) in dietary fat cannot be broken down into fatty acids. Orlistat inhibits the absorption of approximately 30% of dietary fat. This reduces the absorption of fat; undigested fat is then excreted in the feces. Orlistat is absorbed systemically at a minimal level and is mainly metabolized in the gastrointestinal tract; then, most of the drug is excreted unchanged in the feces [5]. It has been
shown that orlistat reduces the incidence of type 2 DM and reduces the levels of total cholesterol and low-density lipoprotein (LDL) cholesterol independent of weight loss [6]. The addition of 120 mg of orlistat 3 times per day to lifestyle changes has been shown to result in significant weight loss [7]. Similarly, data collected from a multi-center clinical study showed that orlistat achieved improvement in terms of obesity, impaired fasting glucose levels, glucose intolerance, and preventing progression to type 2 DM [8].

It has been reported that orlistat interacts with drugs including fatsoluble vitamins, warfarin, amiodarone, cyclosporine, lamotrigine, valproic acid, vigabatrin, gabapentin, and thyroxine. Orlistat can reduce the bioavailability of levothyroxine. Due to its rarity, the cause of this interaction is not yet known, but it is assumed that orlistat may bind to levothyroxine and limit its absorption into the gastrointestinal system [9]. It has also been suggested that orlistat may cause hypothyroidism by reducing the absorption of iodine salts from the gastrointestinal tract [10].

Orlistat is being used intensively for nearly twenty years in obesity treatment in Turkey. However, as far as we know, there is no study investigating the efficacy and safety of the drug in Turkish population. In this study, the effect of 12-week orlistat use on metabolic parameters and TSH in Turkish female patients with obesity was investigated.

Materials and Methods

Study design

The study was designed as a retrospective observational research. Between September 2018 and June 2020, data from 228 patients admitted to the University of Health Sciences Kutahya Education and Research Hospital Endocrinology & Metabolism outpatient clinic, were examined. A total of 100 female patients were included in the study after the exclusion of ineligible patients [Figure 1]. The clinical trial protocol was approved by the ethics committee of the University of Health Sciences, Kutahya Training, and Research Hospital, and complied with the Declaration of Helsinki. (Date: 20.01.2021 No: 2021/01-08).

Eligibility

Inclusion criteria

(a) Female patients aged over 18 years (only female patients were included owing to the fact that the female patients applied more frequently to our outpatient clinic due to obesity than male patients and also on-time arrival of female patients for diet, exercise, medical treatment, and follow-up.) (b) Patients with documented BMI > 40 kg/m² (the reimbursement of orlistat treatment by the social security institution in our country is for the patients with BMI > 40 kg/m²). (c) Patients who do not smoke or consume alcohol, were included in the study.

Exclusion criteria

(a) Patients with an acute coronary syndrome, heart failure, cerebrovascular disease, pregnancy, chronic liver disease, renal function impairment, and cancer. (b) Patients with known or suspected alcohol addiction, using illicit drugs. (c) Patients with disorders of thyroid function tests, on levothyroxine replacement therapy, or anti-thyroid treatment. (d) Patients undergoing obesity surgery. (e) Patients with any endocrinopathy that may lead obesity (Cushing syndrome, hypothyroidism, etc.). (f) Patients taking any medication known to affect body weight. (f) Patients on anti-hyperlipidemic drugs, were excluded from the study.

Figure 1. Flow chart of the study
**Treatment and follow-up**

The height (cm) and body weight (kg) of the patients were measured in the morning after at least ten hours of fasting. BMI (kg/m²) was calculated by dividing the body weight to the square of height in meters. The dietary regulations of the patients were performed every 4 weeks by face-to-face with the dietician. Daily calorie intake was set at 24 calories/kg.

Ideal body weight was calculated by the Devine method [11]. Patients' daily calorie needs were arranged to compose of 50% carbohydrates, 25% fat, and 25% protein. Individuals were encouraged to increase their physical activity. Patients were given diet and exercise programs to ensure spending 300-600 kcal with diet and 200-400 kcal with exercise. Patients were advised to use 120 mg orlistat three times a day immediately after the main meal. The patients in the study stated that they continued their standard diet and exercise programs during the treatment. All patients were followed for 12 weeks. At the baseline, 1st month, 2nd month, and 3rd-month follow-ups; height, weight, and BMI were monitored. Fasting blood glucose (FBG), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, TG, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, insulin, glycated hemoglobin (HbA1c) and Thyroid-stimulating hormone (TSH) levels were measured. Currently used drugs and their doses were not changed during the 12 weeks period of the study.

**Biochemical analysis**

Blood samples were taken at the beginning of the study and after 12 weeks of treatment, in the morning following an overnight fasting for at least 10 hours. Venous fasting blood samples were taken from an antecubital vein in 8 ml evacuated tubes without anticoagulants. The blood in straight tubes was allowed to clot for 30 minutes and centrifuged at 3000 rpm for 10 minutes at room temperature. Repeated freezing and thawing were avoided. Plasma glucose, creatinine, AST, ALT, total cholesterol, TG, HDL, LDL levels were measured by the spectrophotometer method in au5800 series device of Beckman Coulter systems. TSH levels were measured in Beckman Coulter systems DXI 800 device by chemiluminescence method. HbA1c levels were measured by high-performance liquid chromatography (HPLC) method in the TOSOH device.

**Statistical analysis**

Shapiro-Wilk W test was performed to examine the normality of distribution. Descriptive statistical analyses including percent and mean ± standard deviation (±SD) or median (interquartile range [IQR/25- 75] or minimum-maximum), were used to evaluate the basic characteristics of the data, according to the distribution for normality. A paired-samples t-test and Wilcoxon signed ranks test were used for normally distributed continuous variables and non-normally distributed continuous variables, respectively. A repeated-measure ANOVA with a Greenhouse-Geisser correction and post hoc tests using the Bonferroni correction were used to evaluate the difference of weight change by months. Comparison of the BMI values at baseline, 1st, 2nd and 3rd months of treatment was carried out using the Friedman test. All statistical analyses were performed with use of SPSS 23.0 version (IBM Corporation, Armonk, NY, US). Two-tailed p<0.05 was considered to indicate statistical significance.

**Results**

**Baseline characteristics**

The mean age of our patients was 47.1 ± 10.9 years. Mean total cholesterol and LDL cholesterol were 187.5 ± 35.0 mg / dL and 225.9 ± 30.0 mg / dL, respectively. Median creatinine values were 0.76 mg / dL (0.68-0.83) at the beginning of the treatment and decreased to 0.71 mg/dL (0.65-0.80) at the third month of treatment (p <0.0001). Median ALT and AST values were found to be 19.6 U/L (15.2-24.6) and 20.8 U/L (16.9-22.7) at the beginning of the treatment, and 17.4 U/L (13.2-23.1) and 17.1 U/L (15.3-21.1) at the third month of treatment, respectively (p = 0.045 and p = 0.001, respectively). Median TSH values were determined as 1.95mU / L (1.25-2.77) at baseline and 2.05 mU / L (1.62-2.57) at the third month of the treatment (p = 0.071) (Table 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before treatment (baseline)</th>
<th>After treatment (3rd month)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>47.15 ± 10.97</td>
<td>47.15 ± 10.97</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)†</td>
<td>105 (93.2-117.7)</td>
<td>101 (91.2-108.7)</td>
<td>0.001†</td>
</tr>
<tr>
<td>HbA1c , (%)†</td>
<td>5.95 (5.6-6.4)</td>
<td>5.8 (5.5-6.2)</td>
<td>0.001†</td>
</tr>
<tr>
<td>Insulin (mIU/L)†</td>
<td>14 (10.6-18.2)</td>
<td>11.7 (8.2-16.6)</td>
<td>0.001†</td>
</tr>
<tr>
<td>Creatinine (mg/dL) †</td>
<td>0.76 (0.68-0.83)</td>
<td>0.71 (0.65-0.80)</td>
<td>0.001†</td>
</tr>
<tr>
<td>ALT (UI/L) †</td>
<td>19.6 (15.2-24.6)</td>
<td>17.4 (13.2-23.1)</td>
<td>0.045†</td>
</tr>
<tr>
<td>AST (UI/L) †</td>
<td>20.8 (16.9-22.7)</td>
<td>17.1 (15.3-21.1)</td>
<td>0.001†</td>
</tr>
<tr>
<td>Triglyceride (mg/dL) †</td>
<td>149 (106-191)</td>
<td>140 (112.2-182)</td>
<td>0.023†</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL) *</td>
<td>187.5±35.0</td>
<td>182.3±37.6</td>
<td>0.033*</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL) †</td>
<td>49 (40-54)</td>
<td>46 (39-46)</td>
<td>0.001†</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL) *</td>
<td>115.9±30.0</td>
<td>110±31.2</td>
<td>0.019*</td>
</tr>
<tr>
<td>TSH (mU/L)†</td>
<td>1.95 (1.25-2.77)</td>
<td>2.05 (1.62-2.57)</td>
<td>0.071†</td>
</tr>
</tbody>
</table>

HbA1c, glycated hemoglobin; AST; aspartate aminotransferase, ALT; alanine aminotransferase, HDL; high-density lipoprotein LDL; low-density lipoprotein TSH; thyroid-stimulating hormone † Wilcoxon signed ranks test, † Paired samples t-test
* Data are presented as mean ± SD
† Data are presented as median (interquartile range [IQR])
**Glycaemic control**

While the median fasting plasma glucose values were 105 (93.2-117.7) (mg / dL) before treatment, it was 101 (91.2-108.7) mg / dL after the treatment (p <0.0001). Again, the median HbA1c (%) values decreased from 5.95% (5.6-6.4) before the treatment to 5.8% (5.5-6.2) at the 3rd month of the treatment (p <0.0001). In parallel with other glycemic parameters, fasting insulin levels were initially 14 mIU / L (10.6-18.2), whereas it decreased to 11.7 mIU / L (8.2-16.6) after treatment (p <0.0001) [Table 1].

**Serum lipids**

Mean total cholesterol levels were 187.5 ± 35.0 mg / dL before treatment and 182.3 ± 37.6 mg / dL after treatment (p = 0.033). Median serum triglyceride levels were 149 mg / dL (106-191) and 140 mg / dL (112.2-182) before and after treatment, respectively (p = 0.023). Median HDL Cholesterol (mg / dL) levels were 49 mg / dL (40-54) before treatment, while they were 46 mg / dL (39-46) after treatment (p = 0.001). Similarly, a statistically significant decrease was observed in mean LDL-cholesterol (mg / dL) levels from 115.9 ± 30.0 mg / dL before treatment to 110. ± 31.2 mg / dL after treatment (p = 0.019) [Table 1].

**Effectiveness**

In patients receiving orlistat treatment the mean values of body weight (kg) at baseline, 1st, 2nd and 3rd months of the treatment were 110.9 ± 15.7, 107.3 ± 15.2, 105.1 ± 15.1 and 103.3 ± 15.1, respectively (p<0.0001) [Table 2 and Figure 2]. In other words, the mean weight change values at the 1st, 2nd and 3rd months of the orlistat treatment were found as -3.6 ± 0.5 kg, -2.2 ± 0.1 kg, -1.8 kg, respectively (p<0.0001). Median BMI (kg / m²) values at baseline, 1st, 2nd and 3rd months of orlistat treatment were 43.1 (40.0-47.0), 41.7 (39.0-45.4), 40.5 (38.2-44.9) and 39.8 (37.2-44.2), respectively (p <0.0001) [Table 2 and Figure 3].

**Table 2. Weight and BMI changes by months**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1st month</th>
<th>2nd month</th>
<th>3rd month</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight*</td>
<td>110.9 ± 15.7</td>
<td>107.3± 15.2</td>
<td>105.1±15.1</td>
<td>103.3±15.1</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>BMI†</td>
<td>43.1(40.0-47.0)</td>
<td>41.7(39.0-45.4)</td>
<td>40.5(38.2-44.9)</td>
<td>39.8(37.2-44.2)</td>
<td>&lt;0.0001†</td>
</tr>
</tbody>
</table>

BMI; body mass index

* Repeated-measure ANOVA test, † Friedman test

* Data are presented as mean ± SD
† Data are presented as median (min.-max.)

**Safety and adverse events**

No serious drug-related side effects were observed in patients receiving orlistat treatment. Forty-two of the patients (42.0%) had gastrointestinal symptoms related to the pharmacological effects of orlistat, including abdominal bloating, diarrhea, excessive flatulence, steatorrhea, oily spotting, and discharge, which did not require discontinuation of the drug.

**Discussion**

This study was conducted to evaluate the efficacy and safety of orlistat in Turkish female patients with a BMI of > 40 kg/m². It was found that orlistat significantly decreased FBG, insulin, creatinine, AST, ALT, Hba1c, LDL, T. cholesterol, and TG parameters, which are associated with glucose intolerance and risk factors of cardiovascular disease.

Partial inhibition of dietary fat absorption with the gastrointestinal lipase inhibitor orlistat in combination with a hypocaloric diet promotes 5-10% weight loss and improves long-term weight
maintenance in obese individuals [7,8,12]. The lipase inhibitor orlistat has been shown to increase additional weight loss compared to lifestyle changes alone [13]. Orlistat treatment has significantly decreased FPG and HBA1c levels in individuals with or without type 2 DM. Possible mechanisms responsible for this include, a reduction in the percentage of calories absorbed from fat with orlistat therapy, stimulation of glucagon-like peptide-1 (GLP-1) release in the small intestine due to incomplete fat digestion, reduction of post-prandial unesterified fatty acid levels and reduction in visceral adipose tissue [14]. In a 57-week double-blind randomized study of 391 type-2 DM patients with a BMI of 28-40 kg / m² receiving sulfonylurea conducted by Hollander et al., patients were treated with a hypocaloric diet and orlistat 3x120 mg or placebo. It was found that diet and orlistat treatment significantly decreased HbA1c and FPG levels compared to placebo [15]. In a multi-centric placebo-controlled study in which 675 obese patients were recruited, the patients were divided into two groups as placebo and orlistat in addition to the diet, and the patients were monitored for an average of 582 days. Adding orlistat to a conventional weight loss regimen significantly improved oral glucose tolerance and has been found to reduce the rate of progression to impaired glucose tolerance and type 2 DM development [16]. Data from our study showed that improvement in glucose intolerance was due to reductions in body weight. This strongly supports the hypothesis that body weight loss significantly reduces glucose intolerance.

Some studies reported that insulin resistance decreased by 42% measured with the euglycemic hyperinsulinemic glucose clamp technique, by using orlistat 3x120 mg for 3 months in obese patients with insulin resistance [17]. Again, in different studies, it was shown that diet and orlistat treatment provided significant reductions in insulin levels compared to placebo [15,16]. The decrement of serum insulin levels observed in our study may be clinically important since previous studies have associated fasting serum insulin levels with the risk of ischemic heart disease, insulin resistance, and obesity-induced hypertension [18]. The tendency to reduce serum insulin levels suggests that weight loss produced by orlistat, together with diet and lifestyle intervention, may improve insulin resistance syndrome [19].

In meta-analyses, it was found that orlistat treatment significantly reduced LDL cholesterol, Total Cholesterol, and TG levels, which are risk factors for cardiovascular disease [6,20-22]. HDL response to weight loss is extremely varied in meta-analyses, some showing small increases, some no change and some reporting decreases in HDL [22]. It has been confirmed that HDL is poorly associated with weight loss compared to other lipid parameters [22]. Overall, orlistat had no beneficial effects on HDL cholesterol [21,23]. In a meta-analysis by Hu et al., it was found that those who were on a low-carbohydrate diet showed a greater increase in HDL cholesterol but less decrease in LDL cholesterol compared to those on a low-fat diet [24]. It has been reported that weight loss has an increasing effect on HDL levels in the long term, whereas patients who are on a low-fat diet during the weight loss phase may experience a decrease in HDL cholesterol levels [25,26]. In this regard, short-term (3 months) administration of orlistat has been shown to cause a significant reduction in serum HDL cholesterol levels. Orlistat, of which the mechanism of action is inhibiting food-induced fat absorption has probably no effect on HDL cholesterol, which is more likely to be affected by carbohydrate intake rather than fat intake [27,28]. Similarly, in our study, LDL cholesterol, Total Cholesterol, and TG levels of patients receiving orlistat decreased, in accordance with those reported in previous studies. In the current study, the statistically significant decrease in HDL cholesterol levels may be explained with the low-fat diet and weak association of HDL with weight loss. We believe that whether this lowering level of HDL poses any additional risk for cardiovascular diseases should be investigated with further case-controlled studies.

It has been observed in studies and meta-analyses that orlistat treatment reduces the levels of liver function tests: AST and ALT [29,30]. It is thought that orlistat may reduce the damage to hepatocytes by reducing the fat accumulation in the liver and consequently, lowers the aminotransferase levels [31]. In our study, it may be thought that the accumulation of liver fat was decreased due to the weight loss, and secondary to this, there was a decrease in AST and ALT values after orlistat treatment. Similar to liver function tests, in the present study, a significant decrease was found in creatinine levels after orlistat treatment. This situation can be attributed to the decrease in muscle mass resulting from weight loss [32,33].

It has been suggested that orlistat interacts with levothyroxine by reducing its absorption from the gastrointestinal system and it also decreases iodine absorption, with resultant increases in TSH levels. It has been recommended that TSH levels of patients with hypothyroidism and receiving levothyroxine treatment should be closely monitored after orlistat treatment is initiated [34]. In a case report, symptoms and signs of hypothyroidism appeared and TSH was measured as 73.6 mU / L, after orlistat treatment in a patient who received levothyroxine replacement therapy with diagnosis of thyroid papillary cancer. It has been reported that TSH levels return to normal with discontinuation of orlistat treatment [35]. McDuffie et.al. in their study including 20 patients, reported that there was no difference in TSH and free T4 levels after three months of orlistat treatment [27]. As such, in the current study, no effect of orlistat treatment on TSH was observed. Studies on whether orlistat affects TSH levels are limited and case-controlled studies with large participation of patients are needed.

Overall, orlistat is a safe drug, and the frequency of all-grade adverse events (AEs) reported in clinical trials is similar to that in participants treated with placebo. The exception to this is gastrointestinal signs and symptoms, including oily spotting, flatulence, fecal urgency, oily stools, abdominal pain, and fecal incontinence, which are the most commonly reported AEs among orlistat users. The incidence of these AEs rises with the increasing intake rather than fat intake [36] and can be reduced by adding psyllium fiber [37].

The frequency of gastrointestinal AEs have shown to improve over time. Expectedly, apart from mild GIS side effects, no major adverse events were observed in the patients included in our study.

The main limitation of the study is selection bias. In Turkish society, our population was selected from female patients since the admission of the male gender to health institutions due to obesity and the continuity of follow-up are very rare. Other limitations are, single-center participation, lack of control group and retrospective
The results of this study suggest that adding orlistat as a complementary therapy to diet and exercise may be effective in reducing the health risks associated with metabolic diseases caused by obesity. Orlistat could potentially play a vital role in obesity treatment even in early periods.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The clinical trial protocol was approved by the ethics committee of the University of Health Sciences, Kutahya Evílya Celebi Training, and Research Hospital, and complied with the Declaration of Helsinki. (Date: 20.01.2021 No: 2021-01-08).

References