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Comparison of orlistat and orlistat plus metformin therapy between diabetic and nondiabetic groups

Yasemin Emur Gunay[1*], Savaş Volkan Kişioğlu[2], Serdar Karakullukçu[3], Damla Tufekcı[4], Ahmet Suat Demır[4], Hülya Coskun[4], Irfan Nuhoglu[4], Mustafa Kocak[4], Halil Önder Ersöz[4]

SUMMARY

OBJECTIVE: The objective of this study was to examine the effects of orlistat use on metabolic control and weight loss in diabetic and nondiabetic patients.
METHODS: A total of 119 patients with body mass index≥40 kg/m^2 and receiving orlistat therapy, who applied to the Endocrinology polyclinic between January 2016 and October 2019, were included. The patients' weight changes and biochemical values (i.e., fasting glucose, HbA1c, ALT, creatinine, and lipid parameters) were evaluated at the drug beginning and the last polyclinic control. The patients were divided into groups, whether they had diabetes or used metformin, and compared.
RESULTS: The mean age of the 119 patients in the study was 45.3±11.5 years. A total of 94.1% of the patients were females and 5.9% were males. A total of 38.7% of the patients had diabetes and 29.4% had prediabetes. When the patients were compared to whether they had diabetes or used metformin, there was a statistically significant difference between the groups according to weight loss. The mean weight change of patients without diabetes and receiving metformin and orlistat was statistically significantly higher than that of patients with diabetes and receiving metformin and orlistat.
DISCUSSION: It was determined that the weight loss effect of orlistat in obesity was seen in all groups, but this effect decreased in the diabetic group.
KEYWORDS: Obesity. Diabetes mellitus. Orlistat.

INTRODUCTION

Nowadays, obesity has become one of the most critical health problems. Obesity prevalence has tripled in the United States since 1975[1]. Diabetes, metabolic syndrome, cardiovascular diseases, and malignancies such as the esophagus and colorectal cancer, and the mortality rate are related to obesity[2,3].

In our country, orlistat is the only oral agent used in the medical treatment of obesity. Orlistat is a pancreatic lipase inhibitor that temporarily inhibits fat absorption from the gastrointestinal tract and can be used safely for decades without serious side effects[4]. In a meta-analysis of 12 studies involving patients with and without diabetics, lifestyle changes with orlistat treatment resulted in significant weight loss compared to the placebo[5].

Metformin is one of the most commonly used oral antidiabetic agents in treating type 2 diabetes, and it can also be used in prediabetic individuals to retard diabetes progression. Some studies demonstrate that metformin positively affects weight loss due to its mechanism, and some demonstrate a neutral effect[6]. In overweight and obese diabetic patients, 5–10% weight loss improves glycemic control and reduces the need for antidiabetic drugs[7]., although providing weight loss is problematic in diabetic patients due to polypharmacy, weight gain side effects of drugs, and glycemic fluctuations[8].

Our study aimed to examine the effects of orlistat on metabolic control and weight loss in diabetic and nondiabetic patients. However, the comparison of the effects of orlistat plus metformin treatment in prediabetic patients and diabetic patients on weight loss was examined.

METHODS

Study design

In the patients with body mass index (BMI)≥40 kg/m^2 who applied to Karadeniz Technical University Endocrinology and Metabolism Diseases polyclinic between January 2016 and October 2019, those who were received on orlistat (3×120 mg/day) to lose weight were retrospectively screened, and 119 patients were included in the study. Patients with diabetes

[1]Giresun Training and Research Hospital, Department of Endocrinology and Metabolism – Giresun, Turkey.
[2]İstinye University, Faculty of Health Sciences, Yıldızlı Medical Park Hospital, Department of Endocrinology and Metabolism – Istanbul, Turkey.
[3]Karadeniz Technical University, Faculty of Medicine, Department of Public Health – Trabzon, Turkey.
[4]Karadeniz Technical University, Faculty of Medicine, Department of Endocrinology and Metabolism – Trabzon, Turkey.
*Corresponding author: yaseminemurgunay@gmail.com
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whose treatment was changed after starting orlistat therapy and receiving the treatment for less than 3 months were excluded.

It was recorded whether the patients were with or without diabetes. An oral glucose loading test was performed in patients with Hba1c between 5.7 and 6.4% or FG above 100 mg/dL. Patients with impaired FG (100–125 mg/dL) and impaired glucose tolerance (IGT) (140–199 mg/dL) were accepted as prediabetes, and FG≥126 and PPG≥200 were accepted as type 2 diabetes. At the beginning of the treatment, the height (m^2) and weight (kg) of the patients were recorded, and BMI (kg/m^2) was calculated. Weight was measured at the last polyclinic follow-up of the patients. The drug's beginning time and the patients' biochemical values at the last polyclinic follow-up were evaluated (i.e., FG, HbA1c, ALT, creatinine, and lipid parameters). The changes in biochemical and hematological parameters with the treatment were evaluated comparatively at the beginning and the last follow-up.

It was examined whether orlistat use changed in terms of FG, Hba1c, lipid profile, and weight change between the diabetic and nondiabetic groups. The patients were compared by dividing them into three groups according to drug use and the presence of diabetes. Group 1 does not have T2DM but receives orlistat only, Group 2 has T2DM-receiving metformin (2×1,000 mg/day) and orlistat, and Group 3 does not have T2DM but receives metformin and orlistat. It was compared whether the presence of diabetes and the drug use combination made a difference in weight change between the groups.

Biochemical measurement methods

Biochemical parameters were analyzed from plasma samples. Plasma glucose values were measured via hexokinase, which is an enzymatic reference method (Beckman Coulter AU5800). Hba1c was tested via high-performance liquid chromatography (HPLC) and mass spectroscopy (Premier HB9210). Low-density lipoprotein (LDL) was evaluated via the enzymatic calorimetric method (Beckman Coulter AU5800).

Statistical analysis

The SPSS 22.0 statistical package program was used to analyze the data. Descriptive statistics of results are numbers and percentages for categorical variables, namely, mean, standard deviation, median, and minimum-maximum for numerical variables. The Kolmogorov-Smirnov test was used to determine the conformity of the groups to the normal distribution. In comparing numerical variables between two independent groups, the Student's t-test was used when the normal distribution condition was met, and the Mann-Whitney U test was used when it was not. In comparing numerical variables between two dependent groups, the t-test in the dependent groups was used when the normal distribution condition was met, and the Wilcoxon test was used when the normal distribution condition was not met. In comparing three or more independent groups, one-way ANOVA was used when the normal distribution condition was met, and the Kruskal-Wallis test was used when it was not. The chi-square test was used to compare qualitative data. The value $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the 119 patients included in the study was 45.3±11.5 years. A total of 94.1% (n=112) of the patients were females and 5.9% (n=7) were males. The mean baseline BMI was 46.7±6.1. Considering the patients' chronic diseases, 38.7% (n=46) had T2DM, and 50.4% had hypertension. A total of 29.4% (n=35) of the patients received metformin treatment due to prediabetes. The mean duration of drug use of the patients was 7.6±3.4 months. The demographic and clinical characteristics of the patients are given in Table 1.

Table 1. Baseline participant characteristics.

Age (years)	45.3±11.5
Gender	
Female (n%)	112 (94.1)
Male (n%)	7 (5.9)
Weight (kg)	119.4±17.1
BMI (kg/m^2)	46.7±6.1
Diabetes, Yes (n%)	46 (38.7)
Prediabetes, Yes (n%)	35 (29.4)
Prediabetes, No (n%)	38 (31.9)
Hypertension	
Yes (n%)	60 (50.4)
No (n%)	59 (49.6)
Diet compliance	
Complete (n%)	52 (43.7)
Partial (n%)	57 (47.9)
None (n%)	10 (8.4)
Exercise frequency	
More than 3 days a week (n%)	21 (17.7)
Less than 3 days a week (n%)	60 (50.4)
Not exercising (n%)	38 (31.9)
Using metformin	
Yes (n%)	68 (57.1)
No (n%)	51 (42.9)
Drug usage period (months)	7.6±3.4

When the biochemical parameters between the beginning of the treatment and the end of the treatment were examined in all patients, a statistically significant decrease was found in the measured alanine transaminase (p<0.001), triglyceride (TG) (p=0.031), and HbA1C (p<0.001) values (Table 2). Weight changes (pre-post 116–109) and BMI (pre-post 44.9–42.1 kg/m^2) were also found to be significant (p<0.001) (Table 2).

In Table 3, the patients were compared by grouping according to whether they had diabetes and whether they received metformin. Considering the age, there was a statistically significant difference between the groups in terms of mean age (p<0.001). The mean age of patients with diabetes who received metformin and orlistat was significantly higher than in the other groups. In terms of weight change, there was a statistically significant difference between the groups (p=0.030). The mean weight change of patients without diabetes who received metformin and orlistat was statistically significantly higher than that of patients with diabetes who received metformin and orlistat. There was no difference between the groups in biochemical parameters (p>0.05 for each).

A total of 119 patients were included in the study, of whom 94 continued treatment for 6 months, 18 for 9 months, and 36 for 12 months. In all, 29.4% (n=35) of the patients continued the drug for 12 months, 28.6% (n=34) thought it was ineffective, 26.9% (n=32) had problems with drug supply, and 15.1% (n=18) could not use the drug because of side effects (i.e., abdominal pain, nausea, fecal incontinence, etc.)

DISCUSSION

Obesity creates a major metabolic disorder in patients and is a public health problem[8,9]. Our study aimed to compare the effects of orlistat, the only oral obesity drug in our country, in patients with and without diabetes and to understand the effect of adding metformin on weight loss. As a result, it was determined that metformin plus orlistat treatment provided more weight loss in the prediabetic group than in the diabetic group.

In the XENDOS study, which is one of the most extensive studies conducted with orlistat, 3,305 patients with normal FG or IGT were included and lasted for 4 years. In this study, weight loss was significantly higher in patients who received orlistat after treatment. However, the rates of weight loss were similar between groups[10]. In our study, when the results of the 119 patients were evaluated, a significant decrease was found in ALT, TG, and HbA1c after treatment. Body weight and BMI were also decreased from baseline (p<0.05 for each).

When the patients were divided into prediabetic (n=35), diabetic (n=33), and nondiabetic (n=38) groups and compared, weight loss was higher in the prediabetic group receiving orlistat plus metformin treatment compared to the other two groups. Weight loss was statistically higher in the prediabetes group, especially compared to the diabetic group. In addition, 13 patients with diabetes were not received metformin in our study. Weight loss was found to be relatively less in these patients compared to the prediabetic and diabetic groups who received metformin. It demonstrates that orlistat plus metformin treatment significantly affects weight loss in our study. When the ages of the groups were evaluated, it was determined that the diabetic group was older (p<0.05). Although there was no statistically significant difference, the continuation of orlistat was lower in the diabetic group than in the other groups due to side effects, drug supply, and regard as ineffective. Weight loss in diabetic patients is more complicated than in other patients. Although

Table 2. Biochemical changes at the beginning and end of the treatment (all patients).

	At the beginning of treatment	At the end of treatment	p-value
Glucose (mg/dL)	100 (71–305)	99 (70–265)	0.109*
Albumin (g/dL)	4.1 (3.6–5.1)	4.1 (3.4–5.0)	0.501*
Creatinine (mg/dL)	0.7 (0.4–1.8)	0.7 (0.4–1.9)	0.797*
ALT (U/L)[a]	22 (6–153)	19 (5–90)	**<0.001***
Total cholesterol (mg/dL)[b]	199 (92–367)	195 (98–400)	0.668*
TG (mg/dL)[c]	138 (41–768)	124 (48–984)	**0.031***
HDL-C (mg/dL)[d]	45 (29–83)	47 (27–90)	0.369*
LDL-C (mg/dL)[e]	121.6±4.4	119.9±40.7	0.585**
HBA1C (%)[f]	5.9 (4.6–11.7)	5.8 (4.6–11.0)	**<0.001***
Weight (kg)	116 (87–169)	109 (81–170)	**<0.001***
BMI (kg/m^2)[g]	44.9 (40–64.8)	42.1 (30–64)	**<0.001***

*Wilcoxon test and **paired t-test. [a]Alanine transaminase, [b]total cholesterol, [c]triglyceride, [d]high-density lipoprotein cholesterol, [e]low-density lipoprotein cholesterol, [f]hemoglobin A1C, and [g]body mass index. Bold indicates statistically significant values (p<0.05).

Table 3. Evaluation of the change between groups according to drug use status.

	Group 1 (without diabetes, no metformin, only receiving orlistat) (n=38)	Group 2 (with diabetes, receiving metformin and orlistat) (n=33)	Group 3 (without diabetes, receiving metformin and orlistat) (n=35)	p-value
Age (years)	41.6±10.2	51.9±10.2	42.7±11.2	**<0.001** Post hoc: 1-2, 2-,3**
Gender				
Female (n%)	36 (94.7)	32 (97.0)	32 (91.4)	0.682***
Male (n%)	2 (5.3)	1 (3.0)	3 (8.6)	
Glucose (mg/dL)	-1 (-32 to 40)	6 (-80 to 184)	2 (-15 to 37)	0.320*
Albumin (g/dL)	0 (-0.4 to 0.5)	0 (-0.6 to 1)	0 (-0.3 to 0.8)	0.878*
Creatinine (mg/dL)	0 (-0.2 to 0.2)	0 (-0.5 to 0.3)	0 (-0.1 to 0.3)	0.297*
ALT (U/L)[a]	1 (-27 to 42)	4 (-17 to 112)	3 (-37 to 46)	0.419*
Total cholesterol (mg/dL)[b]	9 (-151 to 170)	-7 (-101 to 111)	2 (-106 to 117)	0.178*
TG (mg/dL)[c]	7 (-240 to 140)	19 (-513 to 170)	-2 (-98 to 129)	0.360*
HDL-C (mg/dL)[d]	0.9±6.6	-2.6±9.4	-2.4±6.4	0.088**
LDL-C (mg/dL)[e]	5 (-49 to 143)	-7 (-55 to 102)	1 (-95 to 93)	0.205*
HBA1C (%)[f]	0 (-0.6 to 0.7)	0.2 (-1.8 to 3.4)	0.1 (-0.8 to 0.6)	0.129*
Weight change (kg)	9.2±7.9	6.6±6.0	11.5±8.3	**0.030** Post hoc: 2-3**
Reasons for drug discontinuation (n%)				
Continued	12 (31.6)	7 (21.2)	12 (34.3)	0.305***
Adverse effect	6 (15.8)	7 (21.2)	1 (2.9)	
Providing the drug	10 (26.3)	8 (24.2)	12 (34.3)	
Regarding as ineffective	10 (26.3)	11 (33.3)	10 (28.6)	

*Kruskal-Wallis test, **One-way ANOVA test, and ***Chi-square test. [a]Alanine transaminase, [b]total cholesterol, [c]triglyceride, [d]high-density lipoprotein cholesterol, [e]low-density lipoprotein cholesterol, and [f]hemoglobin A1C. Bold indicates statistically significant values (p<0.05).

the underlying causes are unclear, drugs for blood sugar regulation decrease calorie deficit by reducing glucosuria. At the same time, these drugs themselves (e.g., sulfonylurea, insulin, and beta-blocker) can induce weight gain. Genetic factors of diabetic patients and insulin resistance caused by abdominal obesity complicate weight loss[11]. The multiple drug use to treat diabetes and psychological factors also affect this situation[12]. Although weight loss is difficult, weight loss achieved with orlistat therapy in diabetic patients improves metabolic parameters. In the study conducted by Kelley et al., improvement in glycemic parameters and cardiovascular risk factors was achieved after 1 year of orlistat treatment in patients with type 2 diabetes[13].

While some studies demonstrate that metformin is neutral on weight loss, others state that it has positive aspects. The metformin effect on weight is low in obese patients, such as PCOS with glucose disturbance[14]. The main reasons why metformin causes weight loss are that it increases insulin sensitivity and decreases hepatic gluconeogenesis. In addition, it is thought to have a suppressive effect on the hypothalamic appetite center[15]. The use of metformin in obese patients with insulin resistance reduces hunger by reducing the frequency of postprandial hypoglycemia. At the same time, it increases energy metabolism and physical activity by providing phosphorylation of the AMP protein kinase pathway[16]. In addition, it benefits the anorectic effect by increasing leptin sensitivity; the decrease in ghrelin and the increase in GLP 1 suggest this situation. This increase in GLP 1 contributes to the weight loss effect[17].

Preprandial metformin treatment also increases GLP 1 in diabetic patients, but variations in glucose and insulin levels in the diabetic group affect GLP 1 change[18]. In the 10-year Diabetes Prevention Program Outcome Study (DPPOS), 2,155 patients were randomized, and the effects of metformin on weight change and diabetes occurrence were evaluated. In this study, weight loss was significantly higher than placebo, independently of drug compliance[19]. In another retrospective study, which included 6-month and 1-year follow-ups of diabetic or euglycemic patients, it was

observed that metformin had a weight loss effect[20]. In a study by Sarı et al., it was found that orlistat plus metformin treatment did not provide an additional benefit to only orlistat treatment on weight loss. However, the small number of patients and the 3-month short follow-up period are the negative aspects of the study[21]. In our study, it was concluded that metformin made an additional contribution to orlistat treatment.

CONCLUSION

This study found that the weight loss effect of orlistat in obesity was observed in all groups, but this effect decreased in the diabetic group. The decrease in the weight loss effect of this combination in the diabetic group can be explained by the drug compliance difficulty due to polypharmacy in diabetic patients and resistance that may have developed in the GLP 1 response to metformin. Due to the decrease in the effect of orlistat in the diabetic patient group, another alternative weight loss treatment should be considered in this group. As it is a rare study comparing orlistat and orlistat plus metformin treatment in prediabetic and diabetic populations, it is thought to contribute to the literature.

LIMITATIONS

The study's limitations are retrospective design, its inability to reflect the general population due to the large female population, and the lack of 12-month follow-ups of all patients.

AUTHORS' CONTRIBUTIONS

YEG: Data curaion, Formal Analysis, Resources, Visualization, Writing – original draft. **SVK:** Formal Analysis, Resources, Supervision, Visualization. **SK:** Formal Analysis, Resources, Supervision, Visualization. **DT:** Formal Analysis, Resources, Supervision, Visualization. **ASD:** Formal Analysis, Resources, Supervision, Visualization. **HC:** Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Writing – original draft. **IN:** Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Writing – original draft. **MK:** Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Writing – original draft. **HOE:** Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Writing – original draft.

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