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The comparison of treatment with orlistat and orlistat plus metformin in relation to insulin resistance and weight loss

Işılay Kalan Sarı[1], Serkan Ceylan[2]

[1]University of Health Sciences, Antalya Training and Research Hospital, Department of Endocrinology and Metabolic Disorders, Antalya, Turkey
[2]University of Health Sciences, Antalya Training and Research Hospital, Department of General Surgery, Antalya, Turkey

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ABSTRACT

Introduction: Obesity is a growing health problem. Many drugs have been developed to treat obesity. Orlistat is a widely used drug to treat this disease. Metformin is an antidiabetic drug. Clinicians often prescribe it to treat insulin resistance and achieve weight loss. Our research aims to compare the effects of orlistat alone and its combination with metformin on weight loss and insulin resistance.

Material and Method: This retrospective study was conducted by scanning the data of patients who presented to Antalya Training and Research Hospital Endocrinology, and General Surgery Clinics between 2016 and 2021. 42 morbidly obese patients who met inclusion and exclusion criteria and were prescribed orlistat plus metformin (group 1, n: 28) or orlistat alone (group 2, n: 14) along with a low-calorie diet for three months and were taking it regularly were included. Subsequently, weight, body mass index, fasting blood glucose, fasting insulin, and HOMA-IR (homeostasis model assessment for insulin resistance) were recorded and analyzed at baseline and after three months of taking the medications.

Results: After 3 months of treatment, significant weight loss was achieved in both groups compared to baseline weight (p=0.001 group 1, p=0.003 group 2). HOMA-IR values decreased significantly in both groups (p=0.001 group 1, p=0.01 group 2). Both groups lost the same amount of weight after three months (p=0.06).

Conclusion: In morbidly obese patients without prediabetes or diabetes, the addition of metformin to orlistat therapy did not add benefits in terms of weight loss or insulin resistance.

Keywords: Orlistat, obesity, metformin, insulin resistance

INTRODUCTION

Obesity is a growing health problem (1,2). The risk of diabetes, metabolic syndrome, hypertension, cardiovascular and cerebrovascular disease, gastrointestinal disease, and various malignancies increases with obesity (3). Weight loss of 5% to 10% of body weight is sufficient to reduce morbidity and mortality (1,4,5). Some patients who have difficulty adapting to diet and exercise and do not lose enough weight require medical or sometimes surgical treatment. Orlistat is one of the weight loss agents approved for the treatment of obesity (6). It specifically and effectively inhibits gastric and pancreatic lipase activity in the intestinal lumen and reduces fat absorption from food (7). It binds to the active serine region of gastric and pancreatic lipases via a covalent bond and thus exerts its effect. Therefore, it indirectly leads to weight loss by preventing the formation of monoacylglycerols and free fatty acids and providing a caloric deficit (6). Orlistat exerts all of its pharmacological effects in the gastrointestinal tract and does not alter neurotransmitter levels, as it has no effects on the central nervous system (6). However, the main adverse effects are gastrointestinal. Since orlistat decreases the absorption of fat-soluble vitamins, some associated health problems may occur if the necessary vitamin supply is not provided (6). Through weight loss, orlistat improves lipid profile, blood pressure, fasting blood glucose (FBG), and insulin concentration (8-12). The potential for gastrointestinal discomfort and moderate weight loss may limit the clinical usefulness of the agent. Metformin is an antidiabetic agent that promotes tissue utilization of glucose and decreases insulin resistance (13). Abdominal discomfort, decreased appetite, diarrhea, or constipation are some of the side effects of this drug (13). Weight loss has also been noted

Corresponding Author: Işılay Kalan SARI, isilaykalan@gmail.com
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in patients treated with metformin. However, there are conflicting studies on the effects of metformin on weight loss (13-16). While significant weight loss was achieved with metformin in some studies (13,14), no consistent weight loss was observed in other studies (15,16). The aim of our study is to compare orlistat alone with combined therapy with metformin on body weight and insulin resistance.

MATERIAL AND METHOD

This retrospective study was conducted by scanning data from patients who presented to the Endocrinology and General Surgery Clinics at University of Health Science Antalya Training and Research Hospital between 2016 and 2021. The Ethics Committee of the University of Health Science Antalya Training and Research Hospital approved the study protocol dated June 24, 2021 and No. 9/19, and the report followed the Declaration of Helsinki. Patients were between 18 and 70 years of age, had a BMI (body mass index) ≥40 kg/m², no malignancies, cardiovascular disease, diabetes, or prediabetes (subjects with HbA1c (glycated hemoglobin) <5.7% and FBG <100), who had been taking orlistat regularly for three months or, in the case of insulin resistance, orlistat and metformin, were included in the study. To determine insulin resistance, we used the HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) index and calculated it according to the following formula: HOMA-IR=insulin x FBG (mg/dl)/405. If the value of HOMA-IR was ≥2.7, insulin resistance was assumed (17). As exclusion criteria, we specified that patients were under 18 or over 70 years of age, had a BMI of < 40, were pregnant or breastfeeding, had chronic kidney disease, malignancy, a history of significant cardiovascular disease, diabetes mellitus or prediabetes (FPG ≥100 or HbA1c ≥5.7%), were taking medications that affect glucose metabolism, or had not used orlistat or combination therapy regularly for 3 months. We retrospectively obtained the sex, age, chronic diseases, medications, height, weight, BMI, and laboratory results of patients presenting to our outpatient clinics from their records. We included 42 morbidly obese patients in our study who met the inclusion and exclusion criteria. 28 patients had insulin resistance and were prescribed orlistat 3x120 mg and metformin 2x500 mg and took these drugs regularly for 3 months along with a low-calorie diet (group 1). 14 patients without insulin resistance according to the HOMA-IR index were prescribed orlistat 3x120 mg and took this medication regularly for 3 months along with a low-calorie diet (group 2). We then recorded baseline weight, BMI, FBG, HbA1c, fasting insulin level and after three months of medication. Biochemical tests, including FBG, creatinine, AST, ALT and others, were analyzed by spectrophotometric method using Beckman coulter AU5800 (Beckman coulter Inc. CA, USA) autoanalyzer. Insulin and other necessary hormone tests were analyzed by chemiluminescence method on Beckman coulter DxI800 (Beckman coulter Inc. CA, USA) analyzer. The reference range for fasting insulin in our hospital is 5-35 µU\ml.

Statistical Analysis

We used IBM SPSS version 20 to analyze the data. We used descriptive statistics to define continuous variables (number (n), percentage (%), mean±standard deviation). We performed Student's t-test or Mann-Whitney U-test to compare the two independent groups depending on whether the data were parametric or not. A 'p' value < 0.05 was considered statistically significant.

RESULTS

According to the exclusion and inclusion criteria, the data of a total of 42 patients were fully accessed. The mean age of the patients was 40.6±7.3 years. Thirty cases were female and twelve were male. Twenty-eight subjects were found to have insulin resistance in addition to obesity as established by the HOMA-IR result, and these patients were assigned to group 1. The remaining 14 patients were not found to have insulin resistance, and these patients were assigned to group 2. The mean age of group 1 was 39.9±8.2 years and that of group 2 was 41.1±5.6 years. The age and gender of the two groups were similar (p=0.51 and p=0.92, respectively). The baseline weight of group 1 was 112.6±9.4 kg and that of group 2 was 109.0±11.5 kg. There was no significant difference in baseline weight between the two groups (p=0.06). The baseline value of HOMA-IR was 3.16±1.2 for group 1 and 1.98±0.5 for group 2. The HOMA-IR value was significantly higher in group 1 (p=0.001) (**Table 1**). At the end of the third month, no significant difference was found between the two groups in terms of weight and BMI (p=0.09 and p=0.07, respectively). While weight loss in group 1 was 4.6±2.1 kg, it was 5.2±2.5 kg in group 2. There was no significant difference between the two groups in the amount of weight loss (p=0.06). The HOMA-IR value of group 1 was significantly higher than that of group 2 (2.11±1.5 group 1, 1.45±0.7 group 2) at the end of 3 months (p=0.002) (**Table 2**). Patients in both treatment groups significantly lost weight with these therapies compared to baseline (p=0.001 group 1, p=0.003 group 2). As expected, a significant decrease was observed in HOMA-IR (p=0.001) and FBG (p=0.02) values at the end of 3 months in the group using metformin. However, a significant decrease was achieved in FBG (p=0.04) and HOMA-IR (p=0.01) values at the end of the 3rd month in group 2 who received only orlistat. HOMA-IR was significantly reduced in both groups (p=0.001 group 1, p=0.01 group 2) (**Table 3**).

Table 1. Demographic characteristics and baseline parameters of the patients

	Group 1 (n=28)	Group 2 (n=14)	p
Age (years) (mean±sd)	39.9±8.2	41.1±5.6	0.51
Gender (n/%)			
Male	8 (%28)	4 (%28)	
Female	20 (%72)	10 (%72)	0.92
Body weight (kg) (mean±sd)	112.6±9.4	109.0±11.5	0.06
Body mass index (kg/m²) (mean±sd)	45.5±3.7	44.2±3.1	0.08
Fasting blood glucose (mg/dl) (mean±sd)	90.1±7.9	87.8±9.3	0.98
Fasting insulin (µU/ml) (mean±sd)	13.8±6.6	10.1±3.2	0.002*
HOMA-IR	3.16±1.2	1.98±0.5	0.001*

*<0.05 statistically significant. HOMA-IR; homeostasis model assessment for insulin resistance

Table 2. Control parameters of the patients at the 3rd month after treatment

	Group 1 (n=28)	Group 2 (n=14)	p
Body weight (kg) (mean±sd)	106.0±8.1	104.2±9.5	0.09
Weight loss after 3 months (mean±sd)	4.6±2.1	5.2±2.3	0.06
Body mass index (kg/m²) (mean±sd)	43.2±4.1	42.3±2.9	0.07
Fasting blood glucose (mg/dl) (mean±sd)	85.2±7.5	84.4±8.9	0.62
Fasting insulin (µU/ml) (mean±sd)	9.7±6.3	7.5±2.1	0.008*
HOMA-IR (mean±sd)	2.11±1.5	1.45±0.7	0.002*

*<0.05 statistically significant. HOMA-IR; homeostasis model assessment for insulin resistance

Table 3. Comparison of the parameters of the groups at baseline and after 3 months

	Baseline	After 3 months	p
Body weight (kg) (mean±sd)			
Group 1	112.6±9.4	106.0±8.1	0.001*
Group 2	109.0±11.5	104.2±9.5	0.003*
Body mass index (kg/m²) (mean±sd)			
Group 1	45.5±3.7	43.2±4.1	0.001*
Group 2	44.2±3.1	42.3±2.9	0.005*
Fasting blood glucose (mg/dl) (mean±sd)			
Group 1	90.1±7,9	85.2±7.5	0.02*
Group 2	87.8±9,3	84.4±8.9	0.04*
Fasting insulin (µU/ml) (mean±sd)			
Group 1	13.8±6.6	9.7±6.3	0.001*
Group 2	10.1±3.2	7.5±2.1	0.002*
HOMA-IR (mean±sd)			
Group 1	3.16±1.2	2.11±1.5	0.001*
Group 2	1.98±0.5	1.45±0.7	0.01*

*<0.05 statistically significant. HOMA-IR; homeostasis model assessment for insulin resistance

DISCUSSION

Our study shows that in patients with morbid obesity who do not have prediabetes or diabetes, the addition of metformin to orlistat therapy has no benefit in treating obesity and insulin resistance. As expected, FBG and HOMA-IR levels decreased significantly at the end of the third month in the group receiving combination therapy. However, we observed a significant improvement in insulin resistance and FBG levels, possibly as a result of weight loss in the patients receiving orlistat alone. Obesity is a major cause of hypertension, diabetes, dyslipidemia, and insulin resistance (3). Many drugs have been developed to treat obesity. Orlistat is a drug for the treatment of morbid obesity that reduces cardiovascular risk in these individuals (9,10). This benefit has been reported in some studies as a result of weight loss, but it has also been observed in other studies in which weight loss was not a factor (9,10). In diabetic patients, Kelley et al. (9) observed significant improvement in glycemic parameters and other risk factors for cardiovascular events after 1 year of orlistat treatment, in addition to substantial weight loss. In studies investigating the effects of short-term orlistat use on the risk of cardiovascular events, Bloch et al. observed significant reductions in diastolic blood pressure, FBG, weight, and total cholesterol levels in obese hypertensives after 3 months of orlistat use (12). In previous studies, orlistat treatment increased insulin sensitivity and significantly decreased HOMA-IR (4,5,15). In their study, Heymsfield et al. demonstrated that orlistat prevented the progression of prediabetes and diabetes in obese individuals (5). In the study of Song et al. (18) in obese and overweight women with polycystic ovary syndrome, it is shown that orlistat has fewer side effects and is better tolerated than metformin and provides more benefits in terms of lipid profile and weight loss. Berne et al. (19) showed that orlistat administration in patients with type 2 diabetes resulted in significant improvement in glycemic parameters, insulin resistance, apolipoprotein B levels, and beta cell function, as well as weight loss after approximately 13 months of treatment. We could not investigate other cardiovascular risk factors in our study because it was a retrospective study and patient data were insufficient, but our results are consistent with these studies regarding the benefits of orlistat on weight loss, FBG, and insulin resistance. Metformin may promote weight loss in obese individuals, although some studies have shown no effect in terms of weight. In the study by Kay et al. (23), the metformin group achieved more significant weight loss than the group taking the placebo while in another study, it was observed that taking metformin for six months did not result in noticeable weight loss (16). In another study, weight loss was observed after three months of taking metformin, but it was not statistically significant

(20). Insulin-sensitising drugs such as metformin have been shown in studies to reduce hyperinsulinemia and increase hepatic insulin sensitivity in individuals with obesity, diabetes, or polycystic ovary syndrome, all of which are associated with insulin resistance (16,20). The study conducted by Gokcel et al. (14) showed a significant decrease in weight and HOMA-IR values in individuals treated with orlistat or metformin for six months. In this study, orlistat resulted in a 9.06% weight loss and metformin alone resulted in a 9.90% weight loss. HOMA-IR decreased by 32.73% with orlistat and 39.28% with metformin. We did not include patients taking metformin alone in our study. This is a shortcoming of our study. Therefore, we could not compare the metformin use alone with the orlistat use alone, but we indirectly note that we did not detect any additional effect of metformin in terms of weight, FBG, and insulin resistance. The prospective study by Sari et al. (15) in obese patients showed similar results in terms of insulin resistance or weight loss with the use of orlistat alone and the combined use of metformin and orlistat. These results were consistent with ours. Our study had several limitations. These include its retrospective nature, low metformin dose, small study population, short treatment duration, and lack of overweight and obese groups. Because of the lack of a patient group taking metformin alone and the lack of analysis of other cardiovascular risk factors, it is not possible to comment on the superiority of orlistat over metformin and the benefit of orlistat on other cardiovascular risk factors.

CONCLUSION

Orlistat therapy alone resulted in weight loss and reduced insulin resistance. The addition of metformin to orlistat treatment showed no additional benefit in these parameters. Considering that combination therapy increases costs and side effects, treatment with diet and orlistat might be sufficient to improve insulin sensitivity and lose weight in morbidly obese patients who do not have prediabetes or diabetes.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Antalya Training and Research Hospital Ethics Committee (Date: 24.06.2021, Decision No: 9/19).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Nicklas JM, Huskey KW, Davis RB, Wee CC. Successful weight loss among obese U.S. adults. Am J Prev Med 2012; 42: 481-5
2. Rössner S, Sjöström L, Noack R, Meinders AE, Noseda G. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. European Orlistat Obesity Study Group. Obes Res 2000; 8: 49-61.
3. Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. N Engl J Med 1995; 333: 677-85.
4. Goldstein DJ. Beneficial health effects of modest weight loss. Int J Obes Relat Metab Disord 1992; 16: 397-415.
5. Heymsfield SB, Segal KR, Hauptman J, et al. Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. Arch Int Med 2000; 160: 1321-6.
6. Heck AM, Yanovski JA, Calis KA. Orlistat, a new lipase inhibitor for the management of obesity. Pharmacotherapy 2000; 20: 270-9.
7. Tanakol R. Obezite Tedavisinde Orlistat. Turk Jem 2003; 7: 87-97.
8. Ballinger A. Orlistat in the treatment of obesity. Expert Opin Pharmacother 2000; 1: 841-7.
9. Kelley DE, Bray GA, Pi-Sunyer. Clinical efficacy of orlistat therapy in owerweight and obese patients with insulin treated-type 2 diabetes: a 1-year randomized controlled trial. Diabetes Care 2002; 25: 1033-41.
10. Derosa G, Mugellini A, Ciccarelli L, Fogari R. Randomized, double-blind, placebo-controlled comparison of the action of orlistat, fluvastatin, or both an anthropometric measurements, blood pressure, and lipid profile in obese patients with hypercholesterolemia prescribed a standardized diet. Clin Ther 2003; 25: 1107-22.
11. Muls E, Kolanowski J, Scheen A, Van Gaal L; ObelHyx Study Group. The effects of orlistat on weight and on serum lipids in obese patients with hypercholesterolemia: a randomized, double-blind, placebo-controlled, multicentre study. Int J Obes Relat Metab Disord 2001; 25: 1713-21.
12. Bloch KV, Salles GF, Muxfeldt ES, Da Rocha Nogueira A. Orlistat in hypertensive overweight/obese patients: results of a randomized clinical trial. J Hypertens 2003; 21: 2159-65.
13. Kay JP, Alemzadeh R, Langley G, D'Angelo L, Smith P, Holshouser S. Beneficial effects of metformin in normoglycemic morbidly obese adolescents. Metabolism 2001; 50: 1457-61.
14. Gokcel A, Gumurdulu Y, Karakose H, et al. Evaluation of the safety and efficacy of sibutramine, orlistat and metformin in the treatment of obesity. Diabetes Obes Metab 2002; 4: 49-55.
15. Sari R, Balci MK, Coban E, Yazicioglu G. Comparison of the effect of orlistat vs orlistat plus metformin on weight loss and insulin resistance in obese women. Int J Obes Relat Metab Disord 2004; 28: 1059-63.
16. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Pediatrics 2001; 107: 55.
17. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the study of Insulin Resistance (EGIR). Diabet Med 1999; 16: 442-3.

18. Song J, Ruan X, Gu M, Wang L, Wang H, Mueck AO. Effect of orlistat or metformin in overweight and obese polycystic ovary syndrome patients with insulin resistance. Gynecol Endocrinol 2018; 34: 413-7.
19. Berne C; Orlistat Swedish Type 2 diabetes Study Group. A randomized study of orlistat in combination with a weight management programme in obese patients with Type 2 diabetes treated with metformin. Diabet Med 2005; 22: 612-8.
20. Arslanian SA, Lewy V, Danadian K, Saad R. Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. J Clin Endocrinol Metab 2002; 87: 1555-9.