

The Impact of Orlistat on Diabetic Patients Experiencing Overweight and Constipation: A Randomized Clinical Trial

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Abstract

Objective: Obesity is a global health concern, the use of Orlistat as an anti-obesity drug, has shown promise in managing the constipation and blood sugar levels in diabetic patients. This study aimed to evaluate the impact of Orlistat on diabetic patients experiencing both overweight and constipation.

Materials and Methods: A total of 80 overweight and constipated diabetic patients were randomly enrolled. Participants were randomly assigned to either the intervention or control group. The intervention group received 120 mg Orlistat with lunch for three months, while the control group received placebo, taken once daily with lunch for the same duration. Clinical and paraclinical parameters, including body mass index (BMI), constipation, fasting blood sugar (FBS), HbA1C, triglycerides (TG), cholesterol (CHL), high-density lipoprotein (HDL), creatinine (Cr), aspartate transaminase (AST), alanine transaminase (ALT), and blood sugar two hours postprandial (BS-2HPP), were assessed before and after the intervention.

Results: Significantly, the BS-2HPP and ALT decreased in the intervention group. Additionally, there was a noteworthy improvement in constipation within the intervention group compared to the control group.

Conclusion: Orlistat demonstrates some effectiveness in improving clinical parameters in diabetic patients with obesity and constipation. While the drug shows notable efficacy in alleviating constipation, its impact on other related parameters is not statistically significant. No significant side effects were observed with Orlistat.


Keywords: Diabetes mellitus, Orlistat, Constipation, Obesity, Clinical trial

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Introduction

In recent decades, obesity has emerged as a significant global public health challenge (1). Its deleterious effects extend to various diseases, encompassing type 2 diabetes, liver steatosis, cardiovascular conditions (e.g., high blood pressure, stroke), dyslipidemia, gallbladder disorders, arthritis, sleep apnea, respiratory issues, and several cancers, including endometrial, breast, ovarian, prostate, liver, gall bladder, kidney, colon cancer. This array of health concerns ultimately heightens the risk of mortality (2,3,6,7).

The prevalence of Diabetes Mellitus, a chronic disease, rose from 108 million people worldwide in 1980 to 422 million people in 2014. Projections estimate that by 2045, approximately 700 million adults globally will grapple with diabetes. Alarming increases in diabetes statistics are attributed to lifestyle changes, weight gain, sedentary habits, dietary shifts, heightened reliance on processed foods, and the impacts of the Covid-19 pandemic since 2019, alongside consequential alterations in people's lifestyles (8-14).

On the other hand, constipation, defined by having fewer than three bowel movements per week, is a digestive system disorder. It can stem from immune and nervous system disorders, disturbances in bile acid metabolism, irregular mucus secretion, imbalances in digestive tract microbiota, and fermentation processes. Notably, it is more prevalent in certain diseases such as diabetes mellitus (15).

Orlistat, a potent and selective inhibitor of intestinal lipases, is employed to manage obesity (7). Operating within the gastrointestinal tract lumen, Orlistat forms a covalent bond with gastric and pancreatic lipase, rendering the resulting enzymes inactive. This inhibits the hydrolysis of dietary triglycerides into absorbable free fatty acids and monoglycerides. The non-absorption of undigested triglycerides creates a calorie deficit, positively impacting weight control.

Orlistat exhibits specificity for lipases and exerts minimal inhibitory effects on other digestive enzymes like amylase, trypsin, chymotrypsin, and phospholipases (16).

Widely available over the counter, Orlistat is considered a relatively safe drug, associated with mild to moderate gastrointestinal side effects such as greasy stools, diarrhea, abdominal pain, and stool spotting (16).

Given the escalating challenge of obesity and the consequent rise in the use of anti-obesity drugs, some medications, including Orlistat, are employed in pre-diabetes treatment. Since one of the proven side effects of orlistat is stool softening and steatorrhea, this study seeks to investigate the impact of Orlistat on the symptoms of diabetic patients grappling with both overweight and constipation.

Material and methods

This study employed a randomized clinical trial design with double-blinding. A total of 80 patients diagnosed with type 2 diabetes using purposive sampling, exhibiting both overweight status ($BMI \geq 27$) and constipation (defined as a frequency of defecation less than three times a week), were recruited from the clinic of Shahid Sadouqhi Hospital in Yazd, Iran (16).

Randomization Method: Patients were allocated to either the intervention or control groups utilizing the RAND() function in Excel software. This randomization process occurred in the order of participants' entry into the study, ensuring that each group consisted of 40 individuals.

Blinding Method: To maintain the integrity of the study, a double-blinding approach was implemented. Medications were dispensed in identical and coded containers. Neither the attending physician nor the participating patients were aware of the contents within the containers, thus ensuring a blinded study environment.

Inclusion criteria

- Age between 40 and 55 years.
- Diagnosis of Type 2 diabetes mellitus with overweight, defined as $BMI \geq 27$.
- Presence of constipation, characterized by having less than three bowel movements per week.
- Similar drug-food regimen, with all participants being treated with metformin, empagliflozin, and gliclazide.
- Adherence to a low-calorie and low-fat diet, as recommended for all participants.
- Absence of kidney problems, with a glomerular filtration rate (GFR) greater than or equal to 60.
- No indication of diabetic gastroparesis, as evidenced by the absence of bloating and a heavy feeling in the heart.
- No history of allergy to orlistat.
- Glycated hemoglobin (HbA1c) levels within the range of 5.6 to 8 percent.

Exclusion criteria

- Failure to take prescribed medication for more than three consecutive days.
- Intolerance to the prescribed medication.
- Modification of the patient's medication regimen during the study.
- Aggravation of the disease during the course of the study

Sampling method and determination of sample size

Based on insights from prior studies and aiming for a 10% reduction in the dosage of anti-diabetic drugs and a 50% improvement in constipation, with a maximum standard deviation of 2.5, a significance level of 5%, and a test power of 80%, a sample size of 25 patients was calculated for each group (1-2).

Prescription of medicine

Eligible patients were randomly assigned to either the orlistat or control groups using the RAND function in Microsoft Excel. Each participant was assigned a random number, and then sorted accordingly to allocate them into the orlistat and control groups.

Participants in the orlistat group were administered one 120 mg orlistat capsule daily (Aburaihan, Iran) with lunch for a duration of three months. Conversely, individuals in the control group received a placebo capsule, identical in color and size to the orlistat capsule and containing starch powder, taken with lunch over the same three-month period.

Data collection

Prior to the intervention and three months thereafter, all clinical symptoms and patient characteristics were systematically recorded using a pre-designed checklist. This checklist encompassed demographic details (age, gender, history of underlying diseases, medication history, type of diabetes, etc.) and clinical characteristics (fasting blood sugar, two-hour blood sugar, HbA1C levels, creatinine levels, lipid levels, blood urea nitrogen (BUN), body mass index, and constipation status).

Data analysis

Statistical analysis was performed using SPSS version 26 software. Descriptive statistics such as frequency, percentage, mean, and standard deviation were employed to describe qualitative and quantitative variables. The normal distribution of the data was assessed using the Kolmogorov-Smirnov test (K-S test).

For comparisons between groups, the independent T-test or its non-parametric equivalent was utilized for quantitative data, while the Chi-Square test was applied for qualitative variables. A significance level of $P < 0.05$ was considered to determine the statistical significance of the tests.

Ethical considerations

The study adheres to ethical standards, aligning with the Declaration of Helsinki. Patients were provided with written and informed consent, explaining the study's objectives, procedures, and their right to withdraw at any time.

Approval was obtained from the Research Committee and Ethics Committee of Shahid Sadougi University of Medical Sciences in Yazd, Iran (IR.SSU.MEDICINE.REC.1401.185).

The study is registered with the Clinical Trials Registration Center (IRCT20191106045356N15), and patient information is treated with strict confidentiality. Ethical considerations were paramount throughout the research process, emphasizing participant safety and privacy.

Results

Out of the 400 patients initially evaluated, 80 participants met the inclusion criteria and were included in the study. The participants were evenly distributed, with 40 patients assigned to the intervention group and 40 to the control

group.

However, during the course of the study, 3 patients from the intervention group and 1 patient from the control group were excluded based on the pre-defined exclusion criteria. Ultimately, 76 patients were subjected to statistical analysis upon completion of the study. Among these, 37 patients (48.6%) belonged to the intervention group, and 39 patients (51.3%) were part of the control group (Figure 1).

In this study, the participant demographics revealed a distribution of 10 men (13.1%) and 66 women (86.2%), with an average age of 49.18 ± 2.97 years. The average age for men was 50.0 ± 3.49 years, while women averaged 49.03 ± 2.88 years.

However, the average age of patients in the intervention group (49.35 ± 3.01 years) did not

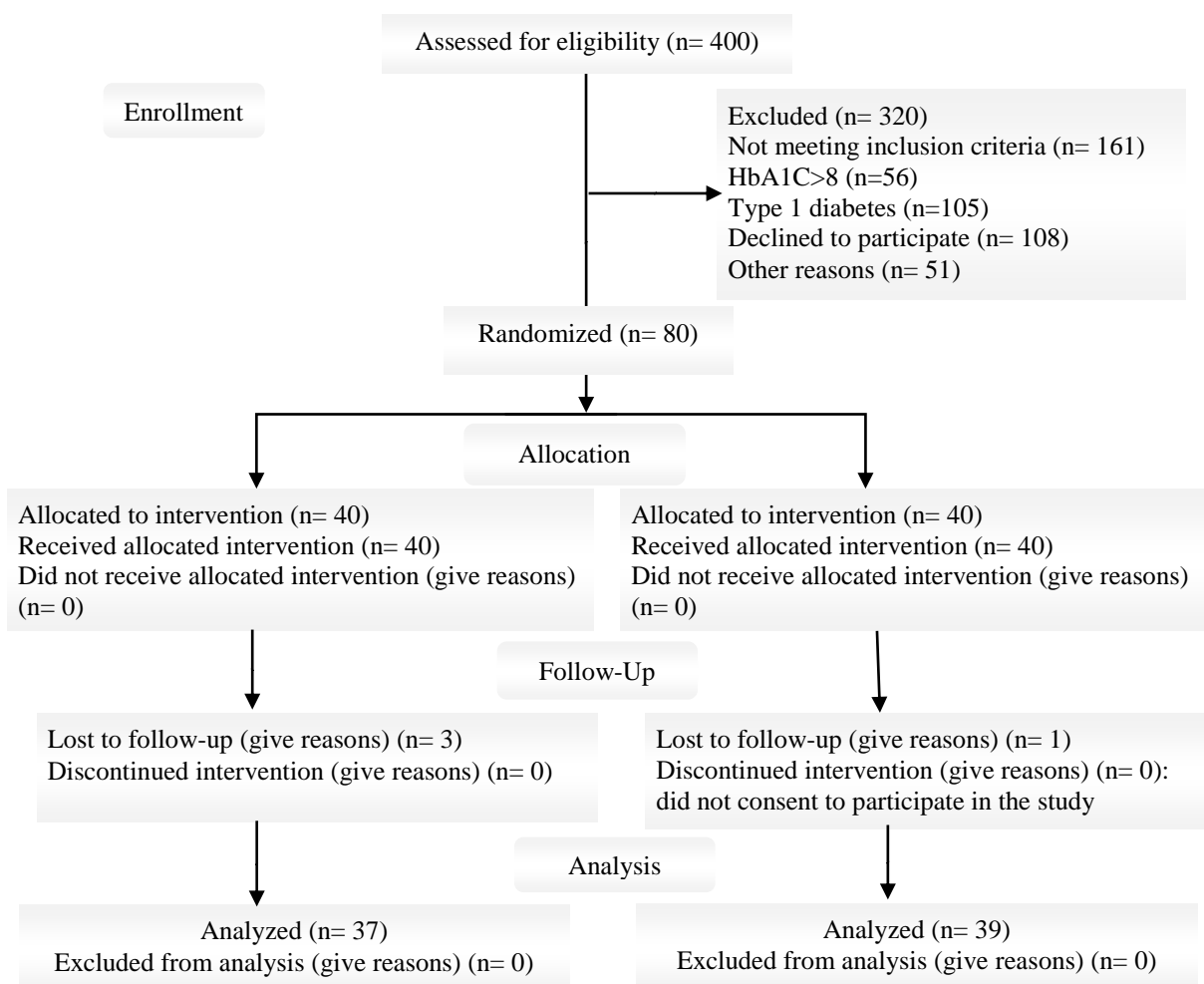


Figure 1. Consort flow diagram

show a significant difference from the control group (49.0± 2.96 years) ($P > 0.05$).

The duration of diabetes of the participants was 4.36± 1.54 years (minimum: 2 years and maximum: 8 years). The duration of the disease in the intervention group was 4.30± 1.58 years (minimum: 2 years and maximum: 8 years) and in the control group it was 4.63± 1.63 years (minimum: 2 years and maximum: 8 year).

No statistically significant difference was observed between the intervention and control groups in terms of the duration of diabetes ($P > 0.05$) (Table 1). The average weight of the patients was 78.27± 7.27 kg (minimum= 68 kg and maximum= 94 kg). The weight of the patients in the intervention group was 78.22± 6.56 kg and in the observation group, it was 78.33± 8 kg. No statistically significant difference was observed between the two groups (P : 0.86). Also, there was no significant difference in the average weight of the patients in the two intervention groups and the control group before and after the intervention (Table 2).

Clinical parameters of patients including FBS, HbA1C, TG, CHL, HDL, Cr, AST, ALT, and BS-2HPP were evaluated as the primary outcomes before and after the intervention in the two intervention and observation groups. The mean and standard deviation of each parameter after the intervention were compared in the two study groups and the results are shown in Table 3.

According to the findings of this study, the average FBS before the intervention did not

show a statistically significant difference between the two intervention groups and the control group ($P > 0.05$).

After the intervention, no statistically significant difference was observed between the two groups in terms of mean FBS ($P > 0.05$). Before the intervention, there was no statistically significant difference in HbA1C between the two intervention and control groups ($P > 0.05$), but after the intervention, this difference was statistically significant ($P < 0.05$).

Regarding the parameters of TG, CHL, HDL, Cr, AST, and BS-2HPP, no statistically significant difference was observed between the target groups before and after the intervention ($P < 0.05$).

Regarding ALT, the investigations showed that the average of this parameter in the two intervention and control groups before the intervention did not have a statistically significant difference ($P > 0.05$), but after the intervention, a statistically significant difference was observed between the two groups ($P < 0.05$). Intra-group comparisons before and after the intervention in the intervention group for HbA1C, CHL, HDL, ALT, and BS-2HPP parameters showed a statistically significant difference ($P < 0.05$), but in the control group, a significant difference was observed only in AST (Table 2).

The findings of this study showed that a statistically significant relationship was observed between constipation and the study group ($P < 0.01$).

Table 1. Demographic factors (Mean ±SD)

Main parameters	Control group (n=39)	Intervention group (n=37)	P-value
Age (years)	49.0 (±2.96)	49.35 (±3.01)	> 0.05
Weight (kg)	78.33 (±8)	78.22 (±6.56)	>0.05
Duration of diabetes (years)	4.63 (±1.63)	4.30 (±1.58)	>0.05

Table 2. Average weight of patients before and after intervention

Variable	Mean ±SD		P-value
	Intervention group	Control group	
Before	78.22 (±6.56)	78.33 (±8)	0.95
After	75.7 (±7.7)	78.17 (±8.92)	0.18
P-value	>0.1	0.85	

The table presents the mean weight of patients before and after the intervention in the intervention, and control groups, with standard deviations (S.D.). P-values indicate the significance of group comparisons.

Table 3. Average and standard deviation of clinical outcomes before and after intervention

Variable		(Mean ± SD)		Mean difference (95% CI)	P-value*
		Intervention	Control		
FBS (Mg/dl)	Before	135.25 (±12.45)	135.36 (±13.44)	-0.10 [-5.91; 5.69]	0.91
	After	132.90 (±17.31)	140.18± 29.90	-7.12 [-17.90; 3.65]	0.26
	Mean Difference 95% CI	2.35 [-3.58; 8.28]	-4.46 [-14.73; 5.81]		
	P-value**	0.13	0.55		
HbA1C	Before	8.01 (±0.29)	7.87 (±0.35)	0.14 [-0.001; 0.28]	0.09
	After	7.65 (±0.45)	7.96±0.69	-0.31 [-0.57; -0.05]	0.02
	Mean Difference 95% CI	0.36 [0.25; 0.48]	-0.09 [-0.27; 0.09]		
	P-value**	<0.001	0.19		
TG (Mg/dl)	Before	206.10 (±39.24)	204.15±37.83	1.30 [-15.80; 18.40]	0.88
	After	195.08 (±29.86)	194.41 (±36.62)	-0.50 [-14.26; 15.26]	0.90
	Mean Difference 95% CI	11.02 [-6.39; 28.44]	10.22 [-3.40; 23.85]		
	P-value**	0.22	0.17		
CHL (Mg/dl)	Before	197.00 (±24.55)	192.87 (±26.14)	3.20 [-8.16; 14.56]	0.75
	After	190.30 (±27.07)	188.15 (±25.24)	1.62 [-10.0; 13.25]	0.47
	Mean Difference 95% CI	6.70 [0.08; 13.31]	5.12 [-1.38; 11.63]		
	P-value**	0.04	0.12		
HDL (Mg/dl)	Before	40.73 (±7.28)	42.13 (±7.31)	-1.65 [-4.91; 1.61]	0.34
	After	43.10 (±6.93)	41.29 (±6.40)	1.57 [-1.55; 4.70]	0.58
	Mean Difference 95% CI	-2.37 [-4.49; -0.25]	0.85 [-0.32; 2.02]		
	P-value**	0.006	0.11		
Cr (Mg/dl)	Before	0.89 (±0.18)	0.85±0.15	0.03 [-0.03; 0.10]	0.31
	After	0.87 (±0.16)	0.89 (±0.14)	-0.02 [-0.09; 0.04]	0.66
	Mean Difference 95% CI	0.02 [-0.05; 0.09]	-0.03 [-0.10; 0.02]		
	P-value**	0.58	0.34		
AST (Unit/L)	Before	31.58 (±9.73)	31.77 (±8.66)	-0.20 [-4.27; 3.87]	0.99
	After	31.10 (±7.55)	28.85 (±10.36)	2.40 [-1.61; 6.41]	0.14
	Mean Difference 95% CI	0.47 [-1.51; 2.46]	3.07 [0.85; 5.29]		
	P-value**	0.76	0.03		
ALT (Unit/L)	Before	36.67 (±12.0)	41.13 (±12.30)	-4.52 [-9.90; 0.85]	0.10
	After	34.23 (±10.59)	39.31 (±13.52)	-5.15 [-10.51; 0.21]	0.005
	Mean Difference 95% CI	2.45 [0.009; 4.90]	1.82 [-1.19; 4.84]		
	P-value**	0.01	0.23		
BS-2HPP (Mg/dl)	Before	205.25 (±35.42)	185.18 (±30.36)	19.45 [4.79; 34.10]	0.01
	After	198.45 (±27.44)	179.46 (±40.31)	18.98 [3.57; 34.40]	0.03
	Mean Difference 95% CI	6.80 [-1.98; 15.58]	7.10 [-6.92; 21.13]		
	P-value**	0.04	0.20		

*Mann-Whitney Test (Between Groups), ** Wilcoxon Signed Ranks Test (Within Group Analysis); FBS: Fasting blood sugar; Hb A1C: Glycated hemoglobin; TG: Triglyceride; CHL: Cholesterol; HDL: High-density lipoprotein; Cr: Creatinine; AST: Aspartate aminotransferase; ALT: Alanine transaminase; BS-2HPP: Blood sugar-two-hour postprandial

Discussion

This study aimed to investigate the impact of Orlistat on the symptoms of diabetic patients grappling with both overweight and constipation. The study indicates that there were no significant differences in demographic factors among patients, such as age, gender, weight, and duration of diabetes in the groups studied. However, after intervention, BS-2HPP and ALT levels showed a significant difference between the groups using orlistat or placebo. Constipation, a key outcome of interest, was less prevalent in the orlistat group compared to the placebo group. Other measured parameters remained unchanged.

Recent studies on orlistat consumption in patients with conditions like obesity, hyperlipoproteinemia, polycystic ovary syndrome, constipation, and polyuria suggest that it generally does not lead to dangerous side effects. However, mild gastrointestinal issues, such as diarrhea, mild abdominal discomfort, and greasy stools, have been reported as common and mild side effects associated with orlistat use (7,17-24).

The 2015 systematic review and meta-analysis by NM Aldekhail et al. focused on the impact of orlistat on blood sugar control in patients with type 2 diabetes and overweight. Out of 765 reviewed articles, 12 randomized clinical trials with a control group were

included. The study reported an average weight loss of 25.4 kg across three time periods: 3 months, 6 months, and one year. This suggests a potential positive effect of orlistat on weight management in individuals with type 2 diabetes and overweight (25).

The first study by NM Aldekhail et al. reported a statistically significant average weight loss difference of 2.10 kg and a significant HbA1C reduction of 6.12% in orlistat intervention groups compared to the control group. However, the study found no significant difference in average fasting blood sugar (FBS) levels before or after the intervention. The conclusion emphasized the potential effectiveness of orlistat in reducing weight and improving blood sugar levels in individuals with diabetes and overweight.

The second study by G Derosa et al. in 2012 involved 254 patients with type 2 diabetes and overweight. It demonstrated that orlistat treatment significantly improved weight loss, fat profile, and body mass index compared to the placebo group. While no significant difference in average blood sugar was observed after intervention, HbA1C showed a significant difference, aligning with the findings of G Derosa et al.'s study (26).

The third study by Giuseppe Derosa et al. in 2011 focused on orlistat combined with l-carnitine in patients with diabetes and obesity. It revealed better and faster improvement in inflammatory parameters for patients treated with orlistat and l-carnitine compared to orlistat alone (27). However, in the present study, only ALT showed a significant decrease after orlistat intervention, with other parameters remaining unchanged. The difference in findings may be attributed to the examination of average parameters over different and longer periods in the mentioned

studies compared to the current study's evaluation at the time of the study.

Conclusion

In conclusion, this study suggests that the use of orlistat in diabetic patients with obesity and constipation may have some positive effects on clinical parameters, albeit not statistically significant when compared to the placebo group for most parameters after intervention. Notably, constipation showed improvement in patients taking orlistat, and no significant side effects associated with orlistat use were observed in the studied patients.

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Conflict of Interest

The authors declare no conflict of interest.

Authors' contributions

Conceptualization, study design, and data analysis: M.Z, A.Gh; Data collection and manuscript writing: F. N. All the authors critically revised the manuscript, agree to be fully accountable for the integrity and accuracy of the study, and read and approved the final manuscript.

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