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Research Article

# Does Orlistat Affect Levothyroxine Bioavailability?

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## Abstract

**Objectives:** Orlistat is used in the treatment of obesity while hypothyroidism is treated with levothyroxine. In this study, the effect of orlistat treatment on thyroid stimulating hormone (TSH) was investigated.

**Methods:** The files of the patients who were followed up with the diagnosis of obesity and hypothyroidism were evaluated retrospectively. Patients with a body mass index (BMI) > 40 and receiving levothyroxine replacement therapy were included in the study. Group 1 consisted of 37 patients who received orlistat and levothyroxine while group 2 consisted of patients who received levothyroxine without orlistat. BMI and TSH values of patients were compared at baseline and at third month.

**Results:** Despite group 1 having mild increase in TSH at third month compared to baseline, no statistically significant difference was observed (p:0.328). No differences were observed between TSH values of group 2 at baseline and third month (p: 0.380). When BMI of group 1 were compared at baseline and third month, it was found to be statistically lower (p<0.01). In group 2, BMI were significantly lower when baseline values were compared with third month (p<0.01).

**Conclusion:** It would be appropriate to closely monitor thyroid function tests in patients on levothyroxine following initiation of orlistat treatment.

**Keywords:** Hypothyroidism, levothyroxine, obesity, orlistat.

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Obesity is defines as an abnormal and over accumulation of body fat tissue which results in deterioration of health. Obesity is second following smoking among the preventable causes of death and a fast growing threat to public health in many countries. Obesity plays a central role in the development of risk factors and chronic diseases that induce cardiovascular morbidity and mortality such as hypertension, dyslipidemia and type-2 diabetes. It is a chronic disease that required treatment due to its effect on the quality of life and problems it induces.[1] Diet, physical activity and behavioural changes with lifestyle changes are the standard first line treatment for obesity. At present, pharmacological treatment of obesity has come into prominence due to failure of classical obesity treatment.[2]

Orlistat is an anti-obesity medication approved by the Food and Drug Administration.[3] Orlistat shows its effect by inhibiting pancreatic and gastric lipase enzymes. Triglycerides taken with dietary fat cannot be separated into fatty acids. It inhibits an average of 30% absorption of dietary fat. It reduces absorption and indigested fat is then excreted with feces.[4]

Hypothyroidism expresses the widespread pathological condition of thyroid hormone deficiency and its prevalence is 5% worldwide. If left untreated, hypothyroidism results in serious

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health problems and even death. Levothyroxine is the accepted as the standard treatment of hypothyroidism.[5,6]

Orlistat has been reported to interact with medications such as lipid soluble vitamins, warfarin, amiodarone, cyclosporine, lamotrigine, valproic acid, vigabatrin, gabapentin and levothyroxine. Orlistat may reduce the bioavailability of levothyroxine. The reason for this interaction is not yet known since its rarity; however, orlistat is assumed to bind with levothyroxine and limit its absorption gastro-intestinal system.[7] Also, orlistat has been suggested to decrease the absorption of iodine salts from gastro-intestinal tract and result in hypothyroidism.[8]

Both obesity and hypothyroidism are prevalent worldwide. The probability of these two diseases co-existing is also highly possible. Only two cases of interaction between orlistat and levothyroxine have been reported and there are no randomized controlled trials.[9,10] In this study, the effect of orlistat treatment on TSH was investigated.

## Methods

### Study Design

The clinical trial protocol was approved by the Ethics Committee of University of Health Sciences, Kütahya Evliya Çelebi Education and Research Hospital (Date: 11.11.2021 Number: 2021/15-25) and complied with the Declaration of Helsinki. It was designed to be a retrospective observational study. The case files of patients that were followed up with the diagnosis of obesity and hypothyroidsm at the University of Health Sciences Kütahya Evliya Çelebi Education and Research Hospital Endocrinology Department between August 2018 and September 2021 were evaluated retrospectively. Patients who complied with follow up visits and medication use were included in the study. Medication compliance was verified by patient declaration and regular medication delivery to patients from their Social Security Agency medulla files. Following exclusion criteria, a total of 37 patients in group 1 that had a body mass index (BMI)>40 and received levothyroxine (25-250 mcg/day) with orlistat 120 mg three times a day (study group) and a total of 40 patients in group 2 that had a BMI>40 and received levothyroxine (25-250 mcg/day) without orlistat (control group) were included in the study (Fig. 1).

### Eligibility

**Inclusion criteria:** (a) Male and female patients aged 18 years and older (b) Patients with BMI >40 (c) Patients who received levothyroxine treatment with the diagnosis of hypothyroidism (d) Patients who complied with diet and medication (e) Patients who complied with regular monthly follow up visits were included in the study.

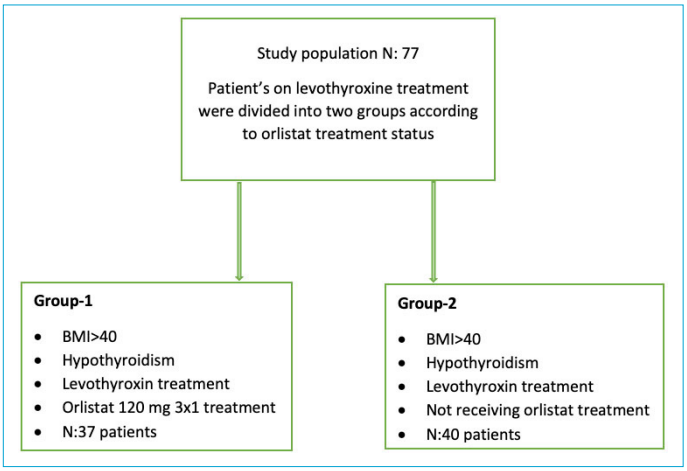


**Figure 1.** Flow chart of study.

BMI: Body Mass Index.

**Exclusion criteria:** (a) Acute coronary syndromes, heart failure, cerebrovascular disease, pregnancy, chronic liver disease, abnormality in renal function tests and malignancy. (b) Patients who were known or suspected to be alcoholic or have illegal drug addiction. (c) Patients with abnormalities in thyroid function tests. (d) Patients with a history of surgery for obesity. (e) Patients with an endocrinopathy that may result in obesity (Cushing's syndrome, acromegaly etc.). (f) Patients known to receive medication which affect body weight (liraglutide, exenatide). (g) Patients on medications that interact with levothyroxine (proton pump inhibitors, iron preparations, calcium preparations etc.). (h) Patients who have a gastrointestinal disease which may affect absorption of medications (gluten enteropathy, crohn disease, ulcerative colitis). (i) Patients who required dose modification for levothyroxine during the 3 months of the study were excluded from the study.

### Treatment and Follow-up

Height and weight of the patients were measured in the morning following at least 10 hours of fasting. BMI (kg/m$^2$) was calculated by dividing weight by the square of height in meters. Diets of the patients were regulated with face to face monthly interviews by a dietician. Daily caloric intake was adjusted to be 24 calories/kg ideal body weight. Ideal body weight was calculated with Devine method.[11] Daily caloric intake of patients were adjusted as 50% carbohydrates, 25% fats and 25% proteins. Individuals were encouraged to increase physical activity. Patients were given diet and exercise program in order to spend 300-600 kcal with diet and 200-400 kcal with exercise. Patients were advised to take orlistat 120 mg three times a day following main meals. Patients in the study declared adhering to regular monthly outpatient visits, diet and exercise programs. Fasting plasma glucose (FPG), creatinine, alanine aminotrans-

ferase (ALT), aspartat aminotransferase (AST), glycosylated haemoglobin (HbA1c), body weight, body mass index (BMI) and thyroid stimulating hormone (TSH) values of all patients were measured and compared at baseline and at third month.

### Biochemical Analysis

Blood samples of the patients were obtained in the morning following at least 10 hours of fasting at baseline and at the third month of the study. Fasting plasma glucose samples of the patients were drawn from antecubital vein to 8 ml emptied anti-coagulant free tubes. Blood samples were allowed to coagulate for 30 minutes and then centrifuged at 3000 rpm at room temperature for 10 minutes. Repeated freezing and defrosting were avoided. Levels of plasma glucose, creatinine, ALT, AST were measured with Beckman Coulter systems au5800 series device by spectrophotometry method. TSH values were measured with Beckman Coulter systems DXI 800 device with chemiluminescence method. HbA1c levels were measured by high performance liquid chromatography (HPLC) method by TOSOH device.

### Statistical Analysis

Normality of distribution was examined by using both the Kolmogorov-Smirnov and Shapiro- Wilk W test. Descriptive statistical methods including percentage and mean ± standard deviation (± SD) was used to provide the basic features of the data, according to the evaluation of distribution for normality. Paired samples t test was used for normally distributed continuous variables (Baseline and third month values for group-1 and group-2 among themselves). Comparisons of the data of the two groups were performed using independent sample t test (Baseline and third month values for group-1 and group-2 between each other). Two-tailed $p<0.05$ was considered to indicate statistical significance.

## Results

### Baseline Characteristics

Median age of patients for group-1 was 54.08±7.58 and 53.68±10.26 for group-2. Thirty two patients in group-1 (86.4%) were female, 5 patients (13.6%) were male and 36 patients (85%) in group-2 were female and 6 patients (15%) were male. There were no statistically significant differences between values of creatinine (mg/dL), ALT (UI/L) and AST (UI/L) in group-1 at baseline and month 3 (p=0.400, p=0.522, p=0.100 respectively) (Table 1). There were also no statistically significant differences between values of creatinine (mg/dL), ALT (UI/L) and AST (UI/L) in group-2 at baseline and month 3 (p=0.500, p=0.388, p=0.053 respectively) (Table 2).

### TSH Values

Patients of group-1 showed no statistically significant differences between TSH (mU/L) values at baseline (2.50±1.07) and third month (2.58±1.06) despite mild increase (p=0.328) (Table 1). Patients of group-1 also showed no statistically significant differences between TSH (mU/L) values at baseline (2.27±0.86) and third month (2.22±0.79) (p=0.380) (Table 2). When baseline TSH values were compared between group-1 and group-2 no statistically significant differences were observed (p=0.290) (Table 3). Similarly, when baseline and third month TSH values were compared between group-1 and group-2 no statistically significant differences were observed (p=0.930) (Table 4).

### Glycemic Control

Fasting plasma glucose values for group-1 at baseline was 103.38±20.43 (mg/dL) and 100.19±21.96 (mg/dL) at third month and 108.45±15.85 (mg/dL) at baseline and 104.05±12.55 (mg/dL) at third month for group-2. When groups were compared among themselves significantly

**Table 1.** Group-1Comparison of baseline and third month values of study group

| Characteristics | Baseline | 3rd month | p |
|---|---|---|---|
| Age, years | | 54.08±7.58 | |
| Sex male/female (%) | | 5/32 (13.6/86.4) | |
| TSH (mU/L) | 2.50±1.07 | 2.58±1.06 | 0.328 |
| Fasting plasma glucose (mg/dL) | 103.38±20.43 | 100.19±21.96 | <0.01 |
| HbA1c (%) | 6.10±0.51 | 5.93±0.51 | <0.01 |
| Creatinine (mg/dL) | 0.78±0.13 | 0.74±0.13 | 0.400 |
| ALT (UI/L) | 25.22±9.68 | 24.30±8.67 | 0.522 |
| AST (UI/L) | 23.73±9.92 | 20.22±4.84 | 0.100 |
| BMI (kg/m$^2$) | 43.64±4.52 | 40.87±4.58 | <0.01 |
| Weight (kg) | 108.09±15.84 | 101.56±14.97 | <0.01 |

HbA1c: glycosylated hemoglobin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TSH: thyroid-stimulating hormone; BMI: body mass index.

**Table 2.** Grup-2 Comparison of baseline and third month values of control group

| Characteristics | Baseline | 3rd month | p |
|---|---|---|---|
| Age, years | | 53.68±10.26 | |
| Sex male/female (%) | | 6/34 (15/85) | |
| TSH (mU/L) | 2.27±0.86 | 2.22±0.79 | 0.380 |
| Fasting plasma glucose (mg/dL) | 108.45±15.85 | 104.05±12.55 | <0.01 |
| HbA1c (%) | 6.29±0.76 | 6.10±0.72 | <0.01 |
| Creatinine (mg/dL) | 0.85±0.14 | 0.86±0.14 | 0.500 |
| ALT (UI/L) | 26.43±8.59 | 25.43±7.60 | 0.388 |
| AST (UI/L) | 23.00±6.02 | 21.40±4.46 | 0.053 |
| BMI (kg/m$^2$) | 44.8±5.25 | 43.6±5.14 | <0.01 |
| Weight (kg) | 113.68±17.05 | 110.96±16.63 | <0.01 |

HbA1c: glycosylated hemoglobin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TSH: thyroid-stimulating hormone; BMI: body mass index.

**Table 3.** Comparison between baseline characteristics of Study Group-1 and Group-2

| Characteristics | Group-1 | Group-2 | p |
|---|---|---|---|
| TSH (mU/L) | 2.50±1.07 | 108.45±15.85 | 0.298 |
| Fasting plasma glucose (mg/dL) | 103.38±20.43 | 100.19±21.96 | 0.226 |
| HbA1c (%) | 6.10±0.51 | 6.29±0.76 | 0.212 |
| Weight | 108.09±15.84 | 113.68±17.05 | 0.142 |

HbA1c: glycosylated hemoglobin; TSH: thyroid-stimulating hormon.

lower values were observed (p<0.01, p<0.01 respectively). Similarly when groups were compared among themselves for HbA1c (%) levels at baseline (grup-1: 6.10±0.5, grup-2: 6.29±0.76) and third month (group-1: 5.93±0.51, group-2: 6.10±0.72) significantly lower values were observed (p<0.01, p<0.01 respectively).

## Effect on Body Weight

While median weight loss at third month in group-1 (group on orlistat) was 6.53 kg, group-2 (group not on orlistat) showed a median weight loss of 2.72 kg. BMI of group-1 was significantly lower when baseline (43.64±4.52) was compared with third month (40.87±4.58) (p<0.01) (Table 1). Similarly, group-2 showed significantly lower third month (43.6±5.14) BMI values when compared with baseline (44.8±5.25) (p<0.01) (Table 2). Both group-1 at baseline (108.09±15.84) and third month (101.56±14.97) (Table 1) and group-2 at baseline (113.68±17.05) and third month (110.96±16.63) (Table 2) showed significantly lower body weight values when groups were compared among themselves (p<0.01, p<0.01 respectively).

## Discussion

Our study showed no statistically significant changes with orlistat use in TSH values despite mild increase.

Two cases were reported on the interaction between levothyroxine and orlistat in literature.[9,10] In one of these cases, the patient was on levothyroxine with the diagnosis of papillary thyroid carcinoma, symptoms and findings of hypothyroidism occurred and TSH was measured to be 73.6 mU/L following orlistat. Following discontinuation of orlistat, TSH were reported to return to normal values.[9] The

**Table 4.** Comparison between baseline characteristics of Study Group-1 and Group-2

| Characteristics | Grup-1 | Grup-2 | p |
|---|---|---|---|
| TSH (mU/L) | 2.58±1.06 | 2.22±0.79 | 0.930 |
| Fasting plasma glucose (mg/dL) | 100.19±21.96 | 104.05±12.55 | 0.342 |
| HbA1c (%) | 5.93±0.51 | 6.10±0.72 | 0.243 |
| Weight | 101.56±14.97 | 110.96±16.63 | 0.011 |

HbA1c: glycosylated hemoglobin; TSH: thyroid-stimulating hormon.

other case was a 43 year old patient. After initiation of orlistat increase in TSH was observed requiring dose increase in levothyroxine. Following discontinuation of orlistat, levothyroxine doses were decreased and TSH returned to normal values.[10]

In a study among 12-16 year old adolescents who were not on levothyroxine and had a BMI: 44,1 (+/- 12,6 kg/m$^2$); orlistat was administered 120 mg 3 times a day, TSH values were compared at baseline and after 3 months. In line with our study, TSH values showed no statistically significant differences following 3 months of orlistat administration.[12]

In literature no studies exist on interaction between levothyroxine and orlistat other than case reports[9,10] mentioned previously. Our study shows originality as it is the first study on this subject.

No common metabolic pathways or plasma protein binding sites were discovered for orlistat and levothyroxine to this day.[10] Close monitoring of thyroid function tests and 4 hour interval between medications is recommended in individuals receiving these two medications.[13] In our study, patients received orlistat 120 mg 3 times per day with meals and levothyroxine 30 minutes before breakfast. Therefore; it is possible that there was less than 4 hours between medications. We did not observe statistically significant differences in TSH values with 3 months of orlistat treatment despite mild increase. Considering the decrease in levothyroxine required especially in patients in the orlistat group due to weight loss of a median 6,53 kg and subsequent decrease in body surface area we believe this mild increase in TSH is significant. In line with literature recommendations that due to rises in TSH values that require levothyroxine dose increase, we also believe close monitoring of thyroid function tests is required when orlistat is used in periods longer than 3 months. Since twice administration of orlistat at noon and in the evening rather than 120 mg 3 times per day provides at least 4 hours of medication interval with levothyroxine administered in the morning on an empty stomach, we believe it would be more appropriate to use orlistat twice a day at noon and in the evening in patients receiving levotyhroxine with the diagnosis of hypothyroidism.

Orlistat has been shown to increase weight loss compared to life style changes. In our study, significant weight loss was observed with diet and exercise both with and without administration of orlistat. However; weight loss was more prominent in the group that was administered orlistat. This finding supports previous literatures.[14]

In a multi-centre placebo controlled trial of 675 obese patients, the patients were divided into two groups of placebo and orlistat in addition to diet and were monitored for 582 days. Oral glucose tolerance significantly improved with the addition of orlistat to conventional weight loss diet and decrease in progression to impaired glucose tolerence and type 2 diabetes mellitus was observed.[15] Data acquired from our study showed that the improvement in glucose tolerance was due to decrease in body weight. This finding supports the hypothesis that weight loss significantly decreases glucose intolerance.

The main limitation of our study is its retrospective design. Low patient numbers, short period of orlistat administration such as 3 months and study being performed in a single centre are other limitations.

In conclusion, when orlistat is commenced in obese patients who receive levothyroxine with the diagnosis of hypothyroidism, a minimum of 4 hour interval between medications and close monitoring of changes in thyroid function tests are required.

#### Disclosures

**Ethics Committee Approval:** The clinical trial protocol was approved by the Ethics Committee of University of Health Sciences, Kütahya Evliya Çelebi Education and Research Hospital (Date: 11.11.2021 Number: 2021/15-25) and complied with the Declaration of Helsinki.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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