

## **The Effect of Betahistine on Body Weight and Waist Circumference in Obese Adults in Comparison with Orlistat** **تأثير علاج البيتاهاستين على وزن الجسم ومحيط الخصر في البالغين البدناء مقارنة بالأورليستات**

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### **Abstract:**

Obesity is a chronic disease in which excess body fat has accumulated and it may affect the health. People who are overweight or obese, compared to those with a healthy weight, are at increased risk for many serious diseases. Two classes of drugs are used in treating obesity: anorexiant and lipase inhibitors. Phentermine and Amfepramone (anorexiant) are indicated for short-term treatment of obesity while orlistat (lipase inhibitors) is approved for long-term treatment, up to 4 years of use.

**Aim of the Study:** The study was designed to assess the effect of betahistine in lowering the body weight and/or decreasing waist circumference.

**Patients and Methods:** The study sample included 60 patients with established overweight or obesity and were divided randomly into 2 groups, 30 patients per group and the body weight and waist circumference were measured every 10 days for 30 days. Each patient was informed about the treatment.

**Results:** In betahistine treatment group, there was a highly significant reduction in body weight and waist circumference after 10, 20 and 30 days compared to baseline levels ( $P < 0.01$ ). In multiple comparisons among orlistat and betahistine groups, there was no significant difference ( $P > 0.05$ ) in body weight and waist circumference after 10, 20 and 30 days of treatment.

**Conclusions:**

Each of orlistat and betahistine exert a reduction effect on body weight and waist circumference. The present study reveals that there are no significant differences between orlistat and betahistine in reducing the body weight and waist circumference.

**Keywords:** orlistat, betahistine, body weight.

### **الملخص :**

السمنة مرض مزمن مصحوب بتراكم الدهون الزائدة في الجسم وقد تؤثر على الصحة. الناس الذين يعانون من زيادة الوزن أو السمنة، مقارنة مع أولئك الذين يعانون من وزن صحي، هم في خطر متزايد للعديد من الأمراض الخطيرة. يتم استخدام فئتين من الأدوية في علاج السمنة: مثبطات الشهية ومثبطات انزيم اللايباز. يشار إلى فينترمين و أمفيبرامون (أنوريكسيانيس) يستخدمان للفتترات قصيرة الأجل من السمنة بينما يتم اعتماد أورليستات لمدة تصل إلى 4 سنوات من الاستخدام.

**الهدف من الدراسة:** بالمقارنة مع استخدام أورليستات في المرضى الذين لديهم مؤشر كتلة الجسم أكثر من 25 تم تصميم هذه الدراسة لتقييم تأثير بيتاهاستين في خفض وزن الجسم وانخفاض محيط الخصر.

المرضى وطرق الدراسة: شملت عينة الدراسة 60 مريضاً يعانون من زيادة الوزن أو السمنة، وتم تقسيمهم عشوائياً إلى مجموعتين، وتم قياس 30 مريض لكل مجموعة ووزن الجسم ومحيط الخصر كل 10 أيام لمدة 30 يوماً. تم إبلاغ كل مريض عن العلاج و أخذ موافقة منهم.

**النتائج:** في مجموعة البيتاهاستين، كان هناك انخفاض كبير جداً في وزن الجسم ومحيط الخصر بعد 10 ، 20 ، 30 يوماً بالمقارنة مع مستويات خط الأساس ( $P < 0.01$ ). في مقارنات متعددة بين البيتاهاستين والأورليستات، لم يكن هناك فرق معنوي ( $P > 0.05$ ) في وزن الجسم ومحيط الخصر بعد 10 ، 20 ، 30 يوماً من العلاج.

**الاستنتاجات:** كل من أورليستات و بيتاهاستين لهما تأثير في تخفيض وزن الجسم ومحيط الخصر. كما وكشفت الدراسة الحالية أنه لا توجد فروق ذات دلالة إحصائية بين أورليستات وبيتاهاستين في تقليل وزن الجسم ومحيط الخصر.

## **Introduction**

Obesity is a complex disease in which additional body fat has accumulated to the level that it may have a negative effect on health. It is commonly present in many countries throughout the world, and its prevalence is increasing in the developed and in developing countries. In fact, obesity is a multifactorial disease that occurs because of the interaction between genotype and environment. Although the etiology of obesity is not well known completely, it involves overlapping of pathophysiology, metabolism, social, behavioral, cultural influence, and genetic composition[1-3].

Obese patients are at increased hazard for many serious diseases and health conditions including mortality, change lipid profile, Type 2 diabetes, cardiovascular disease, gallbladder disease, skin disorder, osteoarthritis, sleep apnea, some cancers, and mental illness (clinical depression, anxiety, and difficulty with physical functioning). The presence of cardiovascular risk factors (cigarette smoking, hypertension) and comorbidities (coronary heart disease, diabetes mellitus) require aggressive management of the overweight or obese patient [4,3].

Generally, two classes of medications are used in treating obesity: anorexiant (phentermine and Amfepramone) and lipase inhibitors (orlistat). Phentermine and diethylpropion are indicated as short-term management while orlistat is approved for up to 4 years of use[3,5].

Betahistine is histamine-like drug, absorbed orally, used in the treatment of symptomatic vestibular disorders[6]. The affinity of betahistine for H1-receptor sites was comparable to that revealed by histamine. Instead of its H1-receptor agonist, it has been shown to be antagonized H3-receptor [7]. Betahistine is licensed for tinnitus, hearing loss associated with Meniere's disease and vertigo. Betahistine has a notable safety profile and several post-marketing assessment constructed by an estimated exposure of approximately more than 130 million patients to betahistine shown a rate of reported side effects to be 1:100 000[8].

Histamine exerts numerous pharmacological effects including change in the neuroendocrine system, feeding behavior, sleep-wake cycles and drinking behavior. The H1 and H3 receptors are important for negative and positive feedback mechanism. Moreover, H3 receptor is an autoreceptor that exists on presynaptic histaminergic cleft and responsible for the regulation of synthesis and release of histamine in the CNS[7]. In other words, when H3 receptor is activated this will lead to decreasing histamine release to the synaptic cleft of histamergic neurons and *vice versa*. Therefore, the antagonistic activity of H3 receptors may be reclassified as inverse agonists[7]. Compared to orlistat used, this study was designed to assess the effect of betahistine in lowering the body weight and/or decreasing waist circumference.

## **Patients and Methods:**

The study sample included 60 patients from Al-Najaf Al-Ashraf Governorate with established overweight or obesity. Samples were collected from November 2016 to the November 2017. Exclusion criteria were patients with past-medical history of heart disease, renal failure, diabetes mellitus or thyroid diseases. Study sample was randomly divided into two groups, 30 patients per group and the body weight and waist circumference were measured every 10 days for 30 days. Each patient was informed about the treatment. **Group I** was treated with orlistat 120 mg, administered orally, twice daily for 30 days interval. **Group II** was treated with betahistine 24 mg, administered orally, twice daily for 30 days interval. Ethical committees of Faculty of Pharmacy, University of Kufa, approved the study protocol.

**Body Mass Index:** BMI is calculated by the following equation:  $BMI = \text{Weight (kg)} / \text{Height (M}^2\text{)}$ [9]. The weights of the patients were measured by using a well-calibrated digital weight scale whereas heights were measured manually.

**Statistical Analysis:** Statistical analyses were performed using SPSS 17.0 for Windows.Inc. Data of quantitative variables were expressed as mean  $\pm$  SEM. Differences in each variable through treatment periods in the same group were compared by using paired-sample Student's t-test. Differences in each variable through treatment periods between different groups were compared by

using independent-sample Student’s t-test. In all tests,  $P < 0.05$  was considered to be statistically significant unless another level was stated.

**Results:**

**Anthropometry:**

The anthropometric data for the 60 obese or overweight patients were taken at first visit as shown in table (1).

**Table (1): Anthropometric data for all included patients of the study (at baseline).**

<b>Anthropometric data</b>	<b>Mean± SEM (Group I)</b>	<b>Mean± SEM (Group II)</b>
<b>Age (year)</b>	31.5± 2.16	<b>34.15± 1.8</b>
<b>Weight ( kg )</b>	101.15±3.5	<b>99.55± 2.92</b>
<b>Height ( cm )</b>	169.65±2.96	<b>173.15± 3</b>
<b>Body Mass Index (kg/m<sup>2</sup>)</b>	35.6± 1.38	<b>33.2± 0.61</b>

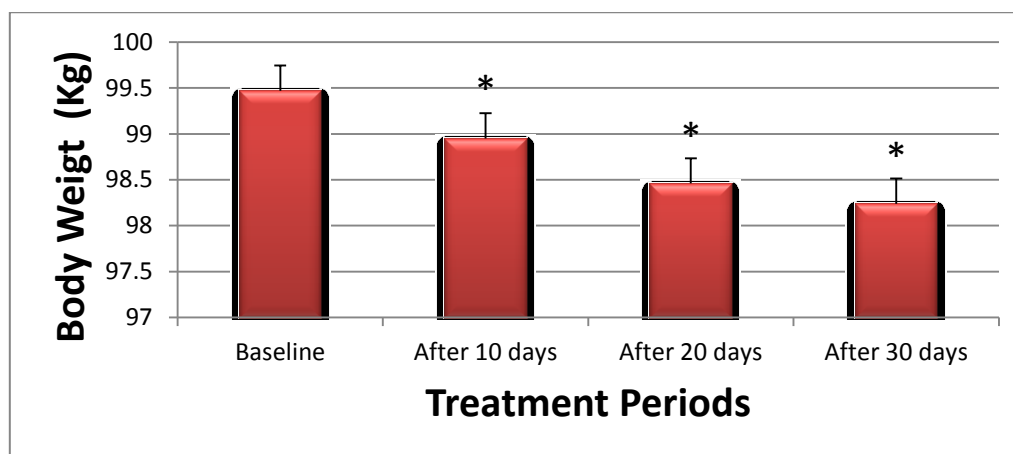
- Values expressed as mean ± SEM

**Group I:** Orlistat treatment group.

**Group II:** Betahistine treatment group.

**The Effect of Orlistat on Body Weight:**

In comparison with baseline levels, there was a highly significant reduction in body weight after 10, 20 and 30 days in orlistat treatment group ( $P < 0.01$ ) as shown in figure (1).



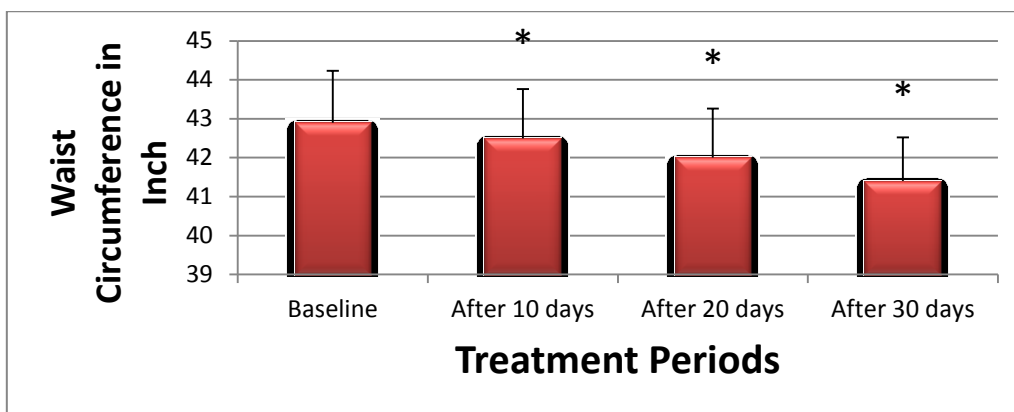
**Figure (1): Mean of changes in body weight after 10, 20 and 30 days compared with baseline value among obese patients in group I.**

\*High significant difference compared to baseline values ( $P < 0.01$ ).

Values expressed as mean ± SEM

**The Effect of Orlistat Treatment on Waist Circumference:**

In comparison with baseline levels, there was a highly significant reduction in waist circumference after 10, 20 and 30 days in orlistat treatment group ( $P < 0.01$ ) as shown in figure (2).



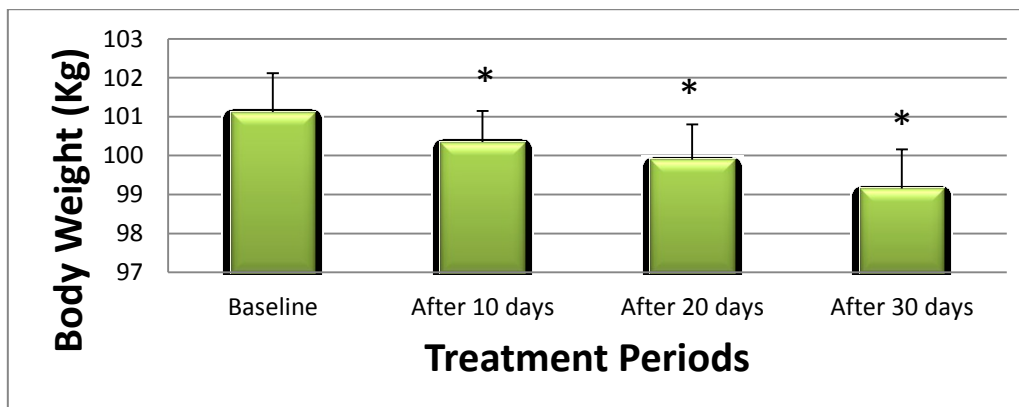
**Figure (2): Mean of changes in waist circumference after 10, 20 and 30 days compared with baseline value among obese patients in group I.**

\*High significant difference compared to baseline values ( $P < 0.01$ ).

Values expressed as mean  $\pm$  SEM

**The Effect of Betahistine Treatment on Body Weight:**

In comparison with baseline levels, there was a highly significant reduction in body weight after 10, 20 and 30 days in betahistine treatment group ( $P < 0.01$ ) as shown in figure (3).



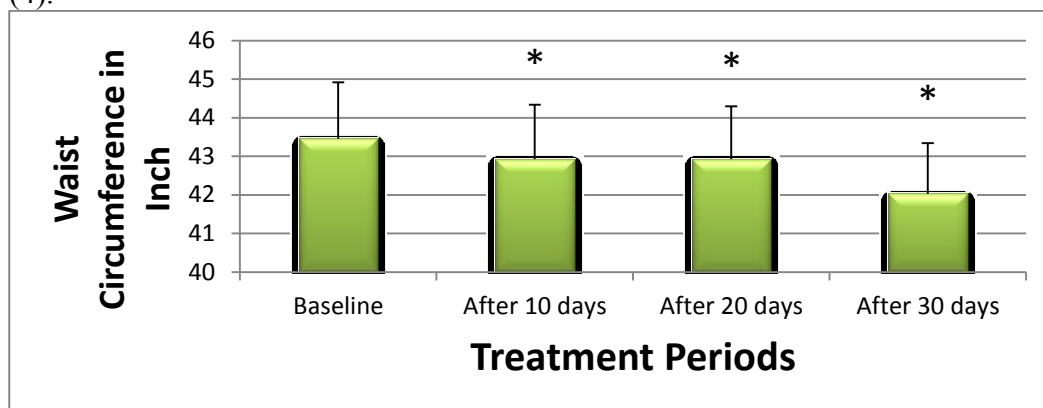
**Figure (3): Mean of changes in body weight after 10, 20 and 30 days compared with baseline value among patients in group II.**

\*High significant difference compared to baseline values ( $P < 0.01$ ).

Values expressed as mean  $\pm$  SEM

**The Effect of Betahistine Treatment on Waist Circumference:**

In comparison with baseline levels, there was a highly significant reduction in wrist circumference after 10, 20 and 30 days in betahistine treatment group ( $P < 0.01$ ) as shown in figure (4).



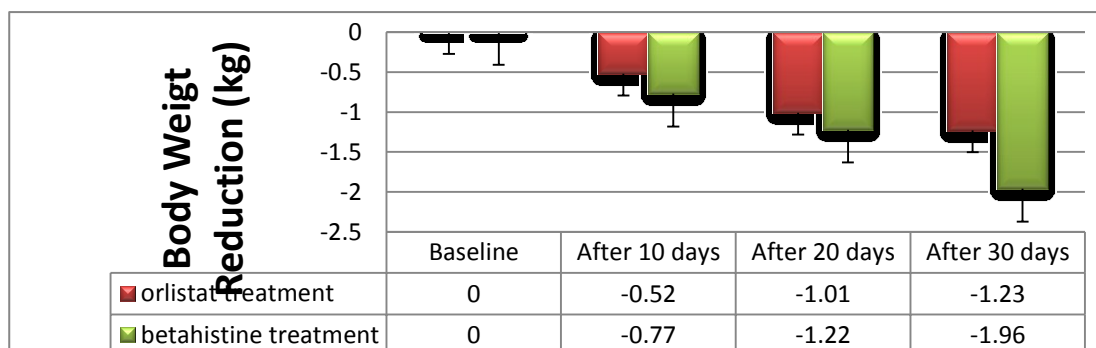
**Figure (4): Mean of changes in waist circumference after 10, 20 and 30 days compared with baseline value among patients in group II.**

\*High significant difference compared to baseline values ( $P < 0.01$ ).

Values expressed as mean  $\pm$  SEM

**The Effect of Different Treatment Groups on Body Weight:**

In multiple comparisons among orlistat and betahistine treatment, there was no significant difference ( $P > 0.05$ ) in body weight reduction after 10, 20 and 30 days of treatment as shown in figure (5).

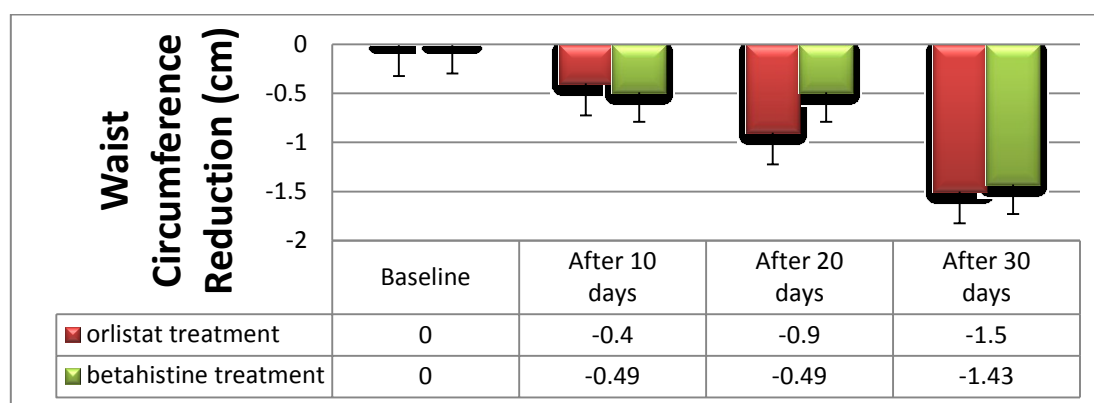


**Figure (5): Mean value differences of body weight reduction in kg between orlistat and betahistine treatment groups.**

\*significant difference compared to group I ( $P < 0.01$ ).

**The Effect of Different Treatment Groups on Waist Circumference:**

In multiple comparisons among orlistat and betahistine treatment, there was no significant difference ( $P > 0.05$ ) in waist circumference reduction after 10, 20 and 30 days of treatment as shown in figure (6).



**Figure (6): Mean value differences of waist circumference reduction in cm between orlistat and betahistine treatment groups.**

\*significant difference compared to group I ( $P < 0.01$ ).

### Discussion:

Obesity is a global problem that is predominantly caused by high calories diet and/or sedentary lifestyle. Most medications used for obesity are approved for short-term treatment because they associated with a high risk of side effects like cardiovascular complications. On the other hand, the lipase inhibitor (e.g, orlistat) is the unique class of medications approved by the FDA for long-term management but its cost has limited its use for many patients[10]. Betahistine is believed to activate H1 receptor and block receptors H3 receptors in the brain that are connected to one's sense of fullness and desire to eat fatty foods. Betahistine has an excellent safety profile and has been used for the treatment by more than 100 million patients suffering from several types of diseases. In the present study, betahistine produces a highly significant reduction in body weight and waist circumference after 10, 20 and 30 days in comparison with baseline; these results support the previous studies that showed the administration of histamine reduces food intake in cats and rats[11]. These findings provide consistent evidence for histamine being an anorexigenic agent and this may be due to H1 and H3 agonist. Several studies showed an involvement of the histaminergic system in the mediation of the anorexigenic effect of leptin and there was a complete absence of an anorexigenic effect of leptin in H1 receptor knockout mice was observed[12]. These observations provide evidence of histamine may act as a mediator of leptin effects. Additionally the effect of histamine on regulation of body weight may be exerted through effects on appetite and direct effects on metabolism. The neuronal histamine has been shown to accelerate lipolysis in white adipose tissue by centrally activating the sympathetic nervous system[13].

As conclusion, each of orlistat and betahistine exert a reduction effect on body weight and waist circumference. Therefore, betahistine had a comparable effect with orlistat (which is a standard medication for obesity) with acceptable side effects and lower cost.

**Conflict of interest:** there is no conflict of interest

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