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Research article

Bromocriptine improves obesity by action on lipid profiles and leptin

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Key words: Obesity, Bromocriptine, Orlistat, Weight loss, Leptin.

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Abstract

Background: Comparative research on the efficacy of a non-prescription drug to support weight loss programmes is currently lacking. This clinical trial compares the lipase inhibitor orlistat and the dopaminergic agonist bromocriptine.
Methods: Seventy-five women with obesity were randomized into three groups according to the treatment received: the obese control group (OC; n = 25), the orlistat group (OR, n = 25, 120 mg capsules, three times a day) and the bromocriptine group (OB, n= 25, 20 mg tablet, once a day). This prospective observational study was conducted with a normocaloric diet for eight weeks. The serum concentration of leptin and the lipid profile were measured, along with the body mass index (BMI) at baseline and after the study.
Results: Bromocriptine treatment (OB) caused a decrease in serum leptin concentration compared to that in the OC and OR groups (ANOVA, $p < 0.01$). Beneficial changes in anthropometric and BMI values were observed following orlistat and bromocriptine administration, with the greatest advantage observed in the OB group.
Conclusions: Beneficial effects were observed on weight loss and body composition in all examined groups, and the greatest improvement in serum leptin was associated with the bromocriptine treatment. We find these strategies promising for the treatment of obesity and its related complications in women.

Introduction

The predominance of obesity has increased globally at an alarming rate, and obesity now considered an epidemic. Obesity has become a significant health concern worldwide because it is associated with a number of fatal metabolic disorders, including diabetes, hypertension, stroke, osteoarthritis, cancer, cardiovascular disease, and sleep breathing disorders [1]. It consumes approximately 2%–6% of the total healthcare expenditure in many developed nations [2]. Obesity, which is characterized by a disproportionate accumulation of fat in the body, is a result of an imbalance in the intake of calories and their utilization by the body. Clinically, a person is considered obese if the body weight is at least 20% higher than average. Overweight is identified by a body mass index (BMI) between 25 and 29.9, while obesity is identified by a BMI higher than 29.9 [3].

Excessive fat storage can cause the inflammation of adipose tissues through macrophage stimulation. This inflammation leads to the release of free fatty acids (FFAs) into the circulatory system, decreased insulin sensitivity and abnormal release of inflammatory adipokines such as interleukin 6 (IL-6), tumour necrosis factor-α (TNF-α), plasminogen activator inhibitor-1 (PAI-1) and monocyte chemoattractant protein-1 [4]. The release of adiponectin, a protective adipokine, also decreases with obesity. Weight loss can reduce some of these metabolic and inflammatory profiles, potentially diminishing the metabolic and cardiovascular risks in obese subjects [5]. In this study, orlistat and bromocriptine were used to reduce the weights of obese adults. Orlistat is a gastrointestinal lipase inhibitor that reduces fat absorption [6], while bromocriptine, a dopamine agonist, affects obese subjects by an unknown mechanism [7].

Hence, the existing study was undertaken to explore the possible weight-lowering action of bromocriptine, which may add to its therapeutic utility. Our objectives were as follows:

•To study the anti-hyperlipaemic activity of bromocriptine.
•To compare its anti-hyperlipemic activity with that of orlistat, which is an established anti-hyperlipemic drug.
•To clarify the underlying molecular mechanisms of action of bromocriptine regarding the level of leptin as a hunger inhibitory adipokine.

Methods

Study design and subjects

A randomized controlled trial was conducted to examine the effects of orlistat and bromocriptine on the BMI, lipid profile, and serum leptin in obese subjects. Obese patients were recruited at the Faculty of Pharmacy, Delta University, Egypt. The study protocol was approved by the Delta University Research Ethics Committee (Human). All subjects signed an informed consent form before any of the study's procedures were performed. One hundred class II obese subjects with body mass indices between 35 and 39.9 kg/m^2 were screened [8] and a total of 75 subjects were recruited. Twenty-five subjects of apparently healthy weight with BMI lower than 25 were included as a healthy control group (Group A). Obese subjects were maintained on a balanced diet and randomly placed into three groups. The first group (Group B) was considered the obese control group and received no treatment (n=25); the second group (Group C) received three daily 120 mg doses of orlistat for eight weeks (n=25) [9]; and the third group (Group D) received one daily 2.5 mg dose of bromocriptine for eight weeks (n=25)[10]. The subjects included in this study were women aged 18—65 years old. None of the subjects had contraindications to the use of orlistat or bromocriptine (e.g., known hypersensitivity to either drug, uncontrolled hypertension, a known history of coronary artery diseases or valvulopathy, a history of severe psychiatric disorders, or prolactinomas), as determined by history, physical examination and blood screening.

All subjects were instructed to maintain their usual physical activity regimen throughout the two-month study. Two months after the beginning of the study, a number of parameters were assessed, namely, BMI, lipid profile and serum leptin.

Determination of body mass index (BMI)

Body mass and height were measured the morning after 14 h of overnight fasting, with an accuracy of 0.1 kg and 0.5 cm, respectively. Body mass index was calculated using the standard formula (weight [kg]/height^2 [m^2]). Obesity was diagnosed according to the criteria set by the World Health Organization [11].

Assessment of lipid profile

Serum triglycerides (TGs), total cholesterol (TC), and high-density lipoprotein (HDL) were assessed by specific enzymatic colorimetric kits obtained from Biodiagnostic Co. (Egypt). Low-density lipoprotein (LDL) was calculated using the following formula (LDL= (TC)-(HDL)-(TG)/5) [12].

Determination of serum leptin

The serum concentrations of the studied adipokine leptin were determined by an ELISA Kit obtained from Glory Science Co., Ltd. (USA). The levels of leptin were expressed in ng/mL.

Statistical analysis

Statistical interpretations were conducted using the Statistical Package for Social Science (SPSS) Software version 21.0 (SPSS, Chicago, IL, USA) and Microsoft Excel (2013). Data are displayed as the mean (±SD). Statistical significance was indicated at $P<0.05$. Reproduced measures analysis of variance (ANOVA) was applied to analyse within- and between-group changes in body mass index, metabolic profile and leptin after eight weeks of orlistat and bromocriptine administration [13].

Results

Body composition measurements

The study was conducted to compare the hypolipidaemic effect of bromocriptine with that of orlistat in obese females. The reduction in BMI was significant in both groups ($P < 0.05$) after 2 months of pharmacological treatment in comparison to both control groups. When the two treated groups were directly compared, no change in BMI was observed (Figure 1).

Lipid index measurements

Orlistat treatment was observed to affect fasting HDL and LDL concentrations. We observed significant increases in HDL levels ($P < 0.05$) in the orlistat-treated group compared to the OC group, but the HDL increase was not significant compared to the level in control group A.

Our results revealed that the orlistat treatment group showed a significant reduction in LDL concentration ($P < 0.05$) in comparison to control group B with obesity.

We also found a slight, though not significant, decrease in TG and TC levels in the orlistat-treated group compared to the control group with obesity.

Bromocriptine treatment produced significant reductions in TC level, TGs, and LDL ($P < 0.05$) compared to the levels in the control group with obesity. Additionally, bromocriptine treatment produced a significant beneficial elevation in HDL concentration ($P < 0.05$) compared to that in the control group of women with obesity. The descriptive effect of orlistat and bromocriptine on the lipid profile is shown in Table 1 and Figure 2.

Effect on serum leptin concentration

The daily administration of bromocriptine daily led to a significant decrease ($P < 0.05$) in serum leptin concentration compared to that in the control group with obesity (group B) (Figure 3).

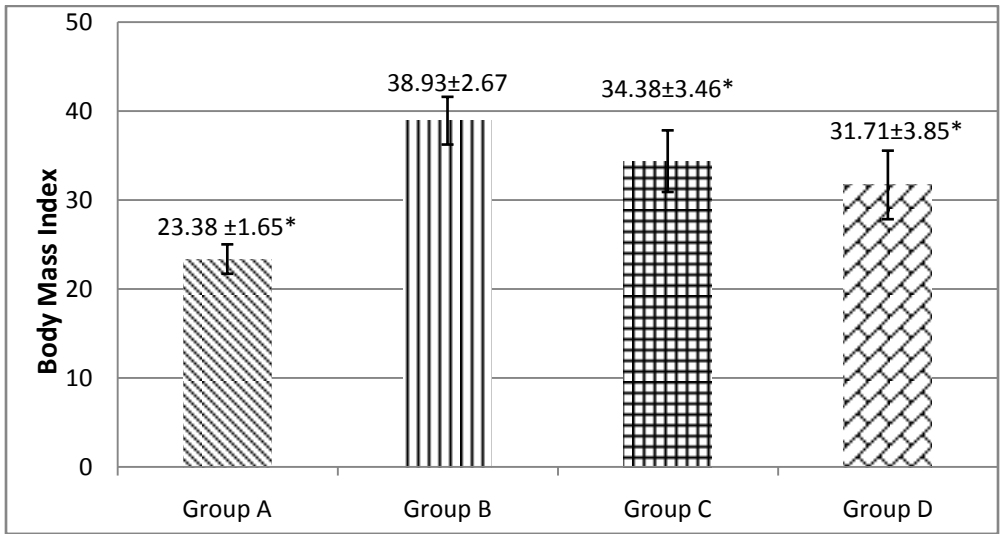

Figure 1. Body mass index measurements after an 8-week period. (Group A) Control group of healthy weight women; (Group B) control women with class II obesity; (Group C) orlistat-treated women; (Group D) bromocriptine-treated women. Each value is the mean ± SD. Error bars indicate standard deviation. *: Significant difference versus group B, P < 0.05.

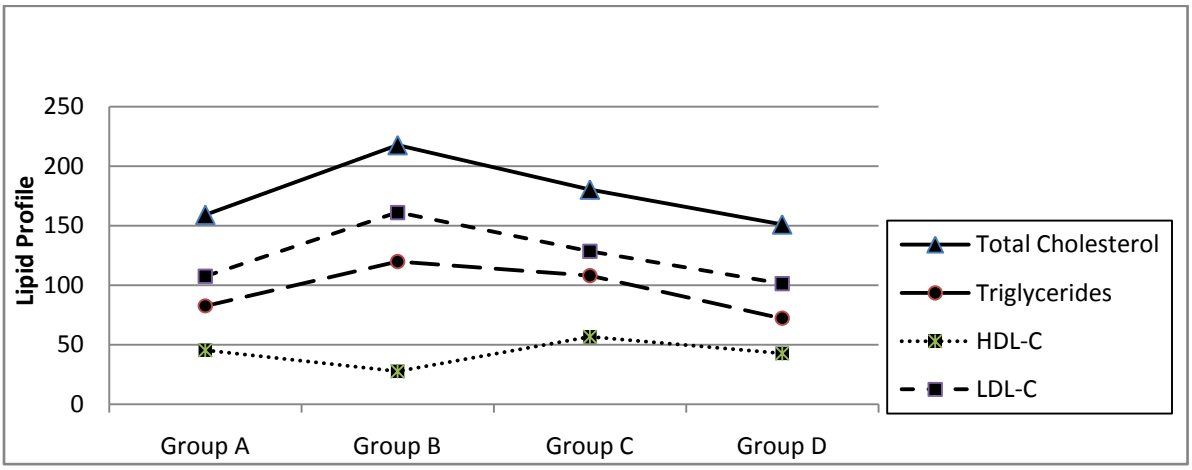

Figure 2. Effect of orlistat and bromocriptine on lipid profile in obese females. (Group A) Control group of healthy weight women; (Group B) control group of women with class II obesity; (Group C) orlistat-treated women; (Group D) bromocriptine-treated women. Each value is the mean for each corresponding group.

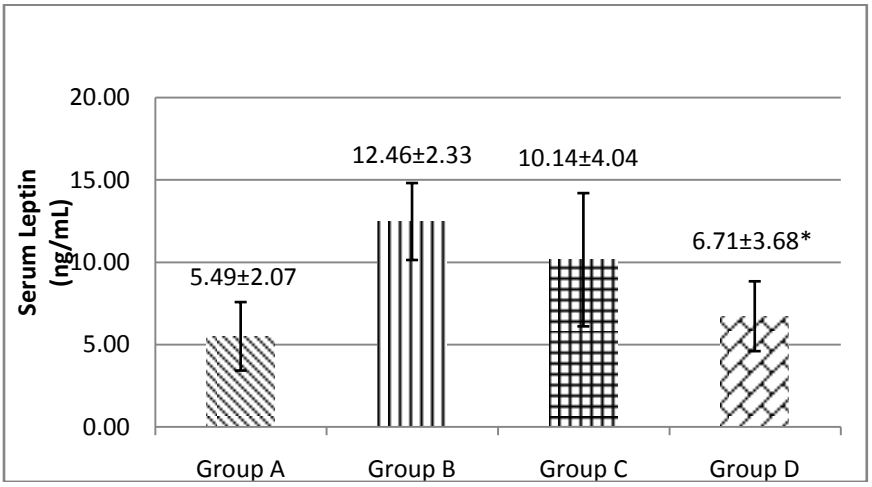

Figure 3. Effect of orlistat and bromocriptine on serum leptin concentration. (Group A) Control group of healthy weight women; (Group B) control group of women with class II obesity; (Group C) orlistat-treated women; (Group D) bromocriptine-treated women. Each value is the mean ± SD. Error bars indicate standard deviation. *: Significant difference versus group B, P < 0.05.

Table 1. Effects of orlistat and bromocriptine on lipid indices in women with obesity.

Variables	Group A	Group B	Group C	Group D
TC (mg/dL)	159.2±19.3*	217.8±51.9	180.4±30.3	151.1±42.9*
TGs (mg/dL)	82.5±22.3*	120±31.9	108.1±31.7	72.1±16.3*
HDL (mg/dL)	45.3±10.9*	27.6±2.3	56.6±9.2*	42.7±8.0*
LDL (mg/dL)	107.4±21.2*	161.2±30.3	128.5±19.2*	101.2±35.3*

(Group A) Control group of healthy weight women; (Group B) control group of women with class II obesity; (Group C) orlistat-treated women; (Group D) bromocriptine-treated women. Each value is the mean ± SD. *: Significant difference versus group B, P < 0.05.

Discussion

This study revealed a new modality for the treatment of obesity through the administration of dopamine agonist therapy. In this comparative study, we assessed the effect of bromocriptine administration on BMI and certain lipaemic parameters. We compared the effect of bromocriptine treatment and a standard weight-reducing treatment, orlistat, in women with class II obesity.

In the current study, orlistat therapy produced significant reductions in BMI and LDL and a substantial increase in HDL without significant effects on TC and TGs compared to those in untreated subjects with obesity. These findings were consistent with the results of other studies that demonstrated that orlistat therapy produced significant body weight reductions in obese patients with further amelioration of lipid profiles, anthropometric measures, and cardiometabolic risk factors [14].

Orlistat leads to the dose-dependent inhibition of intestinal fat absorption through the suppression of intestinal lipase activity [15], which explains the improvement in BMI, HDL and LDL levels.

TG serum levels were not decreased during orlistat therapy in the present study; possible reasons include the hydrolysis of TGs hydrolysed before the inhibition of intestinal lipase by orlistat [16]; the small sample size, which may affect the statistical results; patient non-compliance; or a small dose that may not change high TG levels during the study period.

Therefore, despite the HDL elevation and LDL reduction effect of orlistat on the lipid profile, it failed to reduce TC. These results are incompatible with the findings of the Al-kuraishy and Al-Gareeb study, which revealed a significant improvement in TC levels following orlistat therapy [14]. Additionally, our results are inconsistent with the results of Smith et al., who observed a considerable reduction in TGs following orlistat therapy [17].

The administration of bromocriptine treatment for 8 weeks reduced body weight, BMI, TC, TGs, and LDL; these findings are consistent with a study that showed a significant reduction in TGs and LDL with dopamine agonist treatment [18]. The same research reported non-significant differences in BMI between the dopamine agonist treatment and control groups.

We confirmed that bromocriptine administration improved the lipid profile with weight-reducing effects in obese subjects. The HDL level was elevated. However, our results were opposite to those of some previous studies that reported no significant impact of bromocriptine treatment on the lipid profile [19-20]. The anorexigenic hormone leptin and the orexigenic hormone ghrelin have both been found to have a significant impact on energy balance and obesity. While leptin mediates the long-term regulation of energy balance by suppressing food intake, ghrelin seems to play a role in meal initiation [21].

The abnormally heightened levels of leptin in obese females were not decreased significantly with orlistat treatment. However, the highest significant decrease in leptin was observed in women treated with bromocriptine, who exhibited a leptin level approximately 46% lower than that in the untreated control group with obesity. The decrease in the level of serum leptin may contribute to reduced leptin resistance and improve the anti-obesity effect of bromocriptine treatment. These results are supported by the findings of a previous study showing that dopamine agonist treatment potentiated leptin reduction [22]. On the other hand, our research results contradict the study published by Doknic *et al.*, who reported a gradual increase in serum leptin levels over time in bromocriptine-treated women [23].

Conclusion

The administration of the dopamine agonist bromocriptine leads to a more significant beneficial effect on lipemic parameters than that of orlistat as a weight-loss treatment in patients with class II obesity.Future studies are warranted to investigate the therapeutic efficacy of bromocriptine and orlistat combination againstobesityin clinical settings.

Declaration of interest

The authors declare that no conflict of interest could be perceived as prejudicing the impartiality of the research reported.

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