Improvement of serum adiponectin and leptin concentrations: effects of a low-calorie or isocaloric diet combined with metformin or orlistat – a prospective randomized open-label trial

A. KARGULEWICZ¹, M. SZULIŃSKA², M. KUJAWSKA-ŁUCZAK², E. SWORA-CWYNAŃ¹, K. MUSIALIK², M. GRZYMISŁAWSKA⁴, M. KRĘGIELSKA-NAROŻNA², P. BOGDANSKI²

¹Department of Internal Medicine, Metabolic Disorders and Dietetics, University of Medical Sciences, Poznań, Poland
²Department of Education and Obesity Treatment and Metabolic Disorders, University of Medical Sciences, Poznań, Poland
³Department of Internal Medicine, Metabolic Disorders, and Hypertension, University of Medical Sciences, Poznań, Poland
⁴Department of Anatomy, University of Medical Sciences, Poznań, Poland

Abstract. Objectives: We compared the effects of three weight loss interventions on serum concentrations of adiponectin and leptin in obese premenopausal women.

Patients and Methods: 114 obese Caucasian women were randomized into three groups receiving a low-calorie diet (LC; n = 39), an isocaloric diet with 500 mg of metformin twice a day (IM; n = 38), and an isocaloric diet with 120 mg of orlistat three times a day (IO; n = 37), for three months. Serum concentrations of adiponectin and leptin were evaluated, along with anthropometric and body composition parameters, at baseline and after the study.

Results: Both IO and LC, but not IM, caused an increase in serum adiponectin concentration (p < 0.01, p < 0.05 respectively). A decrease in serum leptin level was documented in the LC (p < 0.001), IM (p < 0.01), and IO group (p < 0.01). Beneficial changes in anthropometric and body composition values were observed following all interventions with the greatest advantage seen in the IO group. The strongest correlations, of Δadiponectin with Δbody weight (r = -0.54), ΔBMI (r = -0.49), ΔFAT [%] (r = -0.48), ΔFAT [kg] (r = -0.48), and Δlean [%] (r = 0.48); and of Δleptin with Δbody weight, ΔBMI, Δwaist, Δfat, and Δlean, were documented in the IO group.

Conclusions: Beneficial effects were observed on serum leptin concentration, weight loss, and body composition for all interventions and in all examined groups, with the greatest advantage being associated with the orlistat treatment. Improvements in serum adiponectin concentrations resulted from the low-calorie and isocaloric diets with orlistat, but not from the isocaloric diet with metformin. We find these strategies more promising for the treatment of obesity and its related complications in obese premenopausal women.

Key Words: Low calorie diet, Metformin, Orlistat, Leptin, Adiponectin.

Introduction

Obesity and overweight have become serious medical problems globally. Central obesity is related to insulin resistance, hyperinsulinemia, and an increased output of proinflammatory cytokines¹,². An excess of visceral fat is associated with the dysregulated secretion of adipokines and may consequently result in vascular dysfunction and overall inflammation³,⁴,⁵.

Leptin was the first adipokine to be identified that derives from adipocytes and is secreted in an amount proportional to the fat mass⁶,⁷. Leptin action affects the regulation of energy intake and expenditure, neuroendocrine function, the metabolism of lipids and glucose, and immunity⁸. Adiponectin is another adipocyte-derived circu-
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Lating hormone that possesses insulin-sensitizing, vascular-protective, and anti-inflammatory properties\(^9\)\(^,\)\(^10\). The concentration of adiponectin has been found to be inversely related to the development of obesity, diabetes mellitus, and hypertension. It has been demonstrated that adiponectin levels are lower in subjects with diabetes and obesity and that higher levels of this adipokine serve as a protective factor against the development of obesity-related complications\(^9\)\(^,\)\(^10\).

The main components of weight loss therapies are based on behavioral changes and include a healthy diet and increasing the frequency of physical activity. However, individuals who are not able to achieve weight loss using lifestyle interventions must instead use pharmacological therapy, including drugs such as the lipase inhibitor orlistat or the insulin-sensitizer metformin\(^11\)\(^-\)\(^13\). It has been demonstrated that both behavioral and pharmaceutical strategies improve adiponectin and leptin profiles in obese subjects\(^14\)\(^-\)\(^17\).

The aim of our study was to compare the effects of three different strategies for weight loss—a low-calorie diet (LC), an isocaloric diet with metformin (IM), and an isocaloric diet with orlistat (IO)—on the serum level of leptin and adiponectin in obese premenopausal women.

**Patients and Methods**

**Study Patients**

The study was approved by the Ethics Committee of Poznań University of Medical Sciences, case no. 688/09. The trial protocol meets the requirements of the Declaration of Helsinki. Of 165 registered patients screened at the outpatient clinic of the Department of Internal Medicine, Metabolism, and Dietetics and the Department of Internal Medicine, Metabolic Disorders, and Hypertension, University of Medical Sciences, Poznań, Poland, a total of 165 obese women were enrolled into the study. Informed consent was obtained from all subjects.

The inclusion criteria were as follows: (1) subjects’ written and informed consent for participation in the study; (2) age from 18 to 40 years; (3) simple obesity (BMI ≥ 30 kg/m\(^2\)); (4) stable body weight for one month prior to the trial (acceptable deviation was ± 1 kg).

The exclusion criteria were: (1) a secondary form of obesity; (2) diabetes mellitus; (3) poorly controlled hypertension (mean systolic blood pressure > 140 mmHg or mean diastolic blood pressure > 90 mmHg) during the month prior to the trial; (4) coronary artery disease; (5) clinically significant arrhythmias or conduction disorders; (6) congestive heart failure; (7) stroke; (8) malignancy; (9) history of use of any dietary supplements in the month prior to the study; (10) abnormal liver, kidney, or thyroid gland function; (11) clinically significant acute or chronic inflammatory process; (12) history of infection in the month prior to the study; (13) nicotine, alcohol, or drug abuse; (14) pregnancy or childbirth at enrollment or in the three months prior to enrollment; (15) lactation at present or in the three months prior to enrollment; (16) menopause; (17) and any other condition that, in the opinion of the investigators, would make participation not in the best interest of the subject.

**Study Design**

The study was designed as a prospective randomized open-label trial comparing a low-calorie diet with and isocaloric diet plus metformin treatment and with an isocaloric diet plus orlistat treatment. All women underwent a three-month run-in period, which started with receiving dietary advice from a qualified dietitian, where they were counseled to adhere to a weight-maintenance (isocaloric) diet. The intake of energy in the isocaloric diet was calculated using the Harris–Benedict equation multiplied with a factor for the physical activity level (PAL). 25% of the total energy was supplied by fat, 20%–25% by protein, and 50%–55% by carbohydrates (Table I). Dietary intake was monitored every 14 days until the end of the trial by a qualified dietitian, on the basis of dietary intake interviews and food diaries. The intake of nutrients, total calories, and caffeine was maintained at a constant level dur-

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<th>Diet component</th>
<th>% of total energy intake</th>
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<td>Carbohydrate intake, of which:</td>
<td>50-55</td>
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<tr>
<td>• Complex carbohydrates</td>
<td>45-50</td>
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<tr>
<td>• Saccharose</td>
<td>&lt; 10</td>
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<tr>
<td>Protein intake</td>
<td>20-25</td>
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<tr>
<td>Fat intake, of which:</td>
<td>25</td>
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<tr>
<td>• Saturated fatty acids</td>
<td>7</td>
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<tr>
<td>• Monounsaturated fatty acids</td>
<td>10</td>
</tr>
<tr>
<td>• Polyunsaturated fatty acids</td>
<td>8</td>
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<tr>
<td>Cholesterol intake [mg/day]</td>
<td>&lt; 300 mg/dL</td>
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</tbody>
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Table I. Composition of diets during the study.
At the baseline and after three months, anthropometric and body composition measurements were made and biochemical parameters were evaluated in the women.

**Anthropometric Parameters**

Anthropometric indices were measured with the subjects barefoot and wearing light clothing. Height was measured to the nearest 0.5 cm and weight to the nearest 0.1 kg. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m²). Obesity was diagnosed with a BMI ≥ 30 kg/m². Waist circumferences were measured to the nearest 0.5 cm midway between the uppermost border of the iliac crest and the lower border of the costal margin the end of normal expiration.

**Body Composition**

Body composition was determined using bioelectrical impedance analysis with a Bodystat analyzer (1500 MDD; Bodystat Ltd., Douglas, Isle of Man). The analysis was performed under stable laboratory conditions after a night’s rest.

**Biochemical Parameters**

Samples of venous blood were drawn from a forearm vein after a 14-hour overnight fast (drinking water was permitted). Adiponectin and
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Leptin serum concentration measurements were estimated by Millipore radioimmunoenzymatic assay (EMD Millipore, St. Charles, MO, USA).

**Statistical Analysis**

The data are presented as means ± SDs. All calculations and demographics were performed using the Statistica 10 software (StatSoft Polska, Sp. z o.o., Kraków, Poland). All changes before and after the intervention were calculated as differences between the final and initial values (with negative values indicating a decrease). The percentage weight and fat loss were calculated as the ratio the change in weight or fat (kg) to the initial weight or fat mass (kg). The chi-square test was used to compare the percentage of weight and fat mass loss in the examined groups. The Shapiro-Wilk test was used to check the normality of the distribution. Comparisons between three groups were assessed using the ANOVA Kruskal-Wallis rank test, or the ANOVA test if the data were normally distributed. The Wilcoxon rank-sum test and the paired t-test (for data with normal distribution) were used to analyze the statistical differences between the variables before and after the intervention. Simple associations between variables were calculated as the Spearman coefficient of correlation. It was determined that a sample size of at least 30 subjects in each group would yield at least an 80% power of detecting an effect as statistically significant at the 0.05 level.

**Results**

Out of the 165 obese patients screened at our outpatient clinic, 8 showed unstable body weight, whereas 37 met the exclusion criteria (2 with secondary hypertension or obesity; 12 with diabetes; 3 with a history of coronary artery disease; 7 with a current need for modification of antihypertensive therapy; 10 with abnormal liver, kidney, or thyroid gland function; 2 with clinically significant inflammatory processes; one with nicotine and alcohol abuse). After screening, 120 women fulfilled all inclusion criteria and none of the exclusion criteria, so they were divided evenly into the LC, IM, and IO groups. One patient from the LC group withdrew her consent, two discontinued the study from IM group (due to loose stools), and three patients from IO group discontinued (due to flatulence). 114 subjects completed the study and no significant changes in diet, physical activity, or medication were recorded in these patients. The analysis was performed in 114 obese women: group LC (n = 39), group IM (n = 38), and group IO (n = 37). A Consolidated Standards of Reporting Trials (Consort) flow diagram is shown in Figure 1.

The baseline anthropometric and biochemical characteristics of the groups are presented in Table II. There were no statistically significant differences in variables between the groups before the study. After three months of intervention, women from all groups exhibited statistically significant and comparable levels of decrease in body weight (LC, p < 0.001; IM, p < 0.001; IO, p < 0.01), BMI (p < 0.01 for LC, IM, and IO group), fat percentage (LC, p < 0.001; IM, p < 0.001; IO, p < 0.01), fat mass (LC, p < 0.05 IM, p < 0.01; IO, p < 0.001), and percentage of lean body mass (LC, p < 0.005; IM, p < 0.01; IO, p < 0.01). The decreases in the percentage weight and fat (kg) were respectively 4.2% and 10.4% in

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group LC</th>
<th>Group IM</th>
<th>Group IO</th>
<th>Difference between groups (p-value)</th>
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</thead>
<tbody>
<tr>
<td>Body weight [kg]</td>
<td>100.65 ± 16.40</td>
<td>108.89 ± 24.06</td>
<td>103.04 ± 17.17</td>
<td>NS</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>36.07 ± 5.62</td>
<td>40.07 ± 8.13</td>
<td>37.03 ± 4.63</td>
<td>NS</td>
</tr>
<tr>
<td>Waist [cm]</td>
<td>104.48 ± 12.94</td>
<td>109.58 ± 16.04</td>
<td>110.31 ± 12.42</td>
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<tr>
<td>Hip [cm]</td>
<td>122.40 ± 9.57</td>
<td>129.05 ± 16.61</td>
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<td>FAT [%]</td>
<td>46.58 ± 5.57</td>
<td>46.61 ± 6.17</td>
<td>45.54 ± 4.72</td>
<td>NS</td>
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<td>FAT [kg]</td>
<td>47.22 ± 10.78</td>
<td>47.18 ± 15.85</td>
<td>47.41 ± 12.21</td>
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<tr>
<td>Lean [%]</td>
<td>55.28 ± 2.50</td>
<td>54.99 ± 5.61</td>
<td>54.28 ± 4.68</td>
<td>NS</td>
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<tr>
<td>Lean [kg]</td>
<td>56.76 ± 9.68</td>
<td>55.60 ± 6.39</td>
<td>54.94 ± 6.14</td>
<td>NS</td>
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<tr>
<td>Leptin [µg/L]</td>
<td>15.64 ± 7.70</td>
<td>14.69 ± 9.29</td>
<td>16.46 ± 9.02</td>
<td>NS</td>
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LC: low-calorie diet; IM: isocaloric diet with metformin; IO: isocaloric diet with orlistat; BMI: body mass index; Waist: waist circumference; Hip: hip circumference; FAT: fat mass; Lean: lean body mass; NS: not significant.
the LC group, 4.5% and 9.1% in the IM group, and 9.4% and 16.5% in the IO group, (p < 0.05 vs. IO group). Significant decreases in anthropometric parameters were noted in all studied groups, including waist circumference. Both the isocaloric diet with orlistat treatment and the standard low-calorie diet caused statistically significant increases in the adiponectin level (p < 0.01 and p < 0.05, respectively). Serum adiponectin concentration remained unchanged after IM treatment. A statistically significant decrease in serum leptin level was documented in the LC group (p < 0.001), the IM group (p < 0.01), and the IO group (p < 0.01). There was no significant difference in the changes (Δ) in the particular parameters among the groups, apart from Δwaist (p < 0.01). Detailed data are shown in Table III.

In the LC group, significant negative correlations were found between Δserum adiponectin and Δwaist (r = -0.39) and ΔFAT [kg] (r = -0.63), whereas Δserum leptin significantly correlated with Δwaist (r = 0.53). In the IM group, Δserum leptin correlated significantly with BMI (r = 0.43 and Δwaist (r = 0.55). In the IO group, Δserum adiponectin significantly correlated with Δbody weight (r = -0.54), ΔBMI (r = -0.49), ΔFAT [%] (r = -0.48), ΔFAT [kg] (r = -0.48), Δlean [%] (r = 0.48), whereas Δserum leptin significantly correlated with Δbody weight, ΔBMI, Δwaist, Δfat, and Δlean body mass (Table IV). As the adiponectin concentration did not change significantly in the IM group, we did not show the correlations between Δserum adiponectin and anthropometry.

**Discussion**

In the prospective randomized open-label trial, we compared diet and pharmacological weight loss approaches to serum adipokines concentrations in premenopausal women with obesity. To our knowledge, this is the first study to compare the effects of a low-calorie diet with an isocaloric diet plus metformin or orlistat on the serum level of adiponectin and leptin in obese premenopausal women. The results indicate that orlistat therapy is an effective method to manage obesity in this population.

The decrease in the mean leptin level was clearest in the IO group, although the decrease in serum leptin concentration was not statistically significant when compared to the remaining groups. The highest drop in plasma leptin

<table>
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<th>Table III. Comparison of parameters before and after interventions in all groups.</th>
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<td>Group LC</td>
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<tr>
<td>Body weight [kg]</td>
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<td>BMI [kg/m²]</td>
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<td>Leptin [µg/L]</td>
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<td>Adiponectin [µg/L]</td>
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LC: low-calorie diet; IM: isocaloric diet with metformin; IO: isocaloric diet with orlistat; BMI: body mass index; Waist: waist circumference; FAT: fat mass; Lean: lean body mass; NS: not significant.
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Concentration for the isocaloric diet plus orlistat group can be explained firstly by the fact that the average weight loss in this group was the highest (though not statistically significantly), and by the fact that the mean weight loss of 5%-10% of initial body mass was the highest for the IO group compared to the others (9.4% vs. 4.2% and 4.5% of the initial body weight). Although maintaining a weight loss of 3% to 5%, it can produce clinically relevant metabolic improvements, larger maintained weight losses reduce cardiovascular risk factors like low-density lipoprotein cholesterol concentration and blood pressure. A 5% to 10% goal is, therefore, recommended for weight loss in obesity treatment. Secondly, the improvements in anthropometric parameters, such as changes in waist circumferences, were found to be significantly greater in the IO group than in the LC and IM groups. This is in agreement with the latest guidelines of the European Association for the Study of Obesity, which indicate that “More attention is to be paid to waist circumference and the improvement of body composition”. In our work, the standard isocaloric diet with metformin or orlistat led to statistically significant decreases in waist circumference, body weight, BMI, and fat mass, and increases in the percentage of lean body mass. However, the most effective method for decreasing weight, fat mass, and waist circumference was the isocaloric diet with orlistat. Moreover, the relationship between changes in anthropometric and body composition parameters and changes in leptin and adiponectin was predominantly observed in the obese women treated with orlistat. Spanos et al. documented a significant decrease in plasma leptin level after 24 weeks of energy restricted diet with orlistat in a group of obese women, and reported a correlation between leptin and BMI and waist circumference, as well as between adiponectin and waist circumference. Thirdly, the effectiveness of orlistat could be explained by its mechanism of action. Orlistat inhibits the activity of gastric and pancreatic lipase in the gastrointestinal tract and thus prevents the absorption of about 30% of ingested fat, leading to a reduction in adipose tissue. Notably, Derosa et al., in a meta-analysis of relevant randomized clinical trials and a systematic review, demonstrated that orlistat is an effective agent for decreasing leptin plasma concentration in patients. It has also been suggested that orlistat acts directly on leptin.

Similarly to leptin, adiponectin concentration was improved after both the isocaloric diet with orlistat and the low-calorie diet alone; there was a statistically nonsignificant advantage to orlistat therapy. Adiponectin is an adipokine which suppresses the risk of the development of the metabolic disturbances of carbohydrate disorders, hyperlipidemia, and fatty liver. In this report, we have demonstrated that a 3-month low-calorie balanced diet led to weight loss and positively influenced serum adiponectin levels in obese women. The mean change in weight loss found was almost comparable between the IM and LC groups. Acharya et al. have provided evidence that weight loss, regardless of diet type and dietary pattern, causes an increase in adiponectin levels. The study of de Luis et al. indicated that both high-protein low-carbohydrate diets and the standard hypocaloric diets produce similar improvements in adipokine levels, despite the greater weight loss that results from the first diet. Other authors have documented that the regulation of adiponectin levels may also be influenced by dietary patterns.

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BMI: body mass index; Waist: waist circumference; Hip: hip circumference; WHR: waist–hip ratio; FAT: fat mass; Lean: lean body mass; asterisks refer to statistical significant correlations (p < 0.05).
frequency of ingested meals caused a significantly greater increase in adiponectin levels than did the consumption of only three meals and two snacks per day. This association has not been demonstrated by other authors. de Luis et al documented no statistically significant changes in the concentration of adiponectin in obese males and females after two months of hypocaloric diet. Pharmacological interventions were also beneficial. An increase in adiponectin levels in obese women after three months of treatment with orlistat was reported by Tzoiou et al. In the research of Bougoulia et al, a hypocaloric diet and a hypocaloric diet with orlistat led to significant improvements in adiponectin concentrations after six months of intervention in obese women of childbearing age. Similar improvements in plasma adiponectin were presented in a systematic review and meta-analysis published by Derosa et al. The results obtained may depend on the duration of the intervention. Another mechanism for the increase in adiponectin is the influence of orlistat on circulating lipopolysaccharides by affecting intestinal microbiota.

Our findings showed that the intervention with the isocaloric diet and metformin decreased serum leptin but did not change serum adiponectin concentrations. Nar et al observed that both metformin and the energy-restricted diet equally reduced BMI and leptin in newly diagnosed type-2 diabetic patients with nonalcohol liver steatosis. Possible mechanisms of action include the effect of metformin on peptides regulating food intake, including leptin, adiponectin, ghrelin, and neuropeptide Y. Metformin, an insulin sensitizer, reduces fat mass and thus decreases leptin secretion. It may also improve leptin hypothalamic sensitivity and thus reduce the level of circulating leptin.

Metformin appears to promote adiponectin expression and multimerization through mechanisms independent of nuclear receptor peroxisome proliferator-activated receptors γ. However, the exact influence of metformin on the expression and secretion of adiponectin may be tissuespecific and has yet to be elucidated. The data showing elevated adiponectin levels after metformin treatment mostly derive from studies on women with polycystic ovary syndrome (PCO). Increased adiponectin concentrations following metformin treatment were observed after six months of intervention in obese and nonobese women with PCO and in obese postmenopausal women with type-2 diabetes during a six-month trial. Unfortunately, our findings did not confirm these results. The shorter duration of metformin treatment in our study may have led to this discrepancy.

Varady et al have demonstrated that the minimal weight loss required to obtain an improvement in the adipokine profile is 5% from baseline. It is worth emphasizing that, according to our findings, 4.2% weight loss from baseline is sufficient to cause a reduction in serum leptin and an increase in serum adiponectin concentrations in the studied population.

The fact that the study was of the open-label type, rather than a blind trial, may be considered a limitation of the study. The use of higher doses of metformin may produce more informative results. The treatment time should be prolonged to observe further effects of the intervention, particularly with respect to metformin treatment.

Conclusions

Our study provides evidence for the beneficial effects of all three interventions, including a low-calorie diet and an isocaloric diet combined with metformin or orlistat, on serum leptin concentration, with parallel decreases in body weight and improvements in body composition in obese premenopausal women.

Significant increases in serum adiponectin concentrations resulted from the low-calorie diet or orlistat regimen, but not from the metformin treatment, indicating that these strategies are useful in the treatment of obesity and its complications.

As young and middle-aged women are a target of weight-loss interventions, further long-term studies are needed to evaluate the long-term effects of orlistat and metformin treatment on body composition, adiponectin profile, and cardiometabolic risk.

Acknowledgements

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Conflict of Interest

The Authors declare that there are no conflicts of interest.
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