Endocrine (2015) 49:286–289
DOI 10.1007/s12020-014-0426-4

RESEARCH LETTER

Effect of orlistat on weight loss, hormonal and metabolic profiles in women with polycystic ovarian syndrome: a randomized double-blind placebo-controlled trial

Ashraf Moini · Mahia Kanani · Ladan Kashani · Reihaneh Hosseini · Ladan Hosseini

Received: 25 April 2014 / Accepted: 5 September 2014 / Published online: 8 October 2014

Introduction

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism and chronic anovulation. This disorder is estimated to affect 5–10 % of women of reproductive age [1]. PCOS is strongly associated with obesity and metabolic syndrome components.

It is believed that PCOS and obesity exacerbate one another in a number of ways [2]. Insulin resistance caused by obesity is one reason for hyperinsulinemia which can subsequently stimulate ovarian androgen synthesis [3–7]. Additionally, vaspin, an insulin-sensitizing adipokine visceral adipose tissue-derived serine protease inhibitor has been shown to cause an increase in PCOS and play a role in androgen excess, abdominal adiposity, and insulin resistance [8]. Therefore, many of these women face weight loss challenges that are attributed to long-term disturbances in hormonal patterns and inappropriate nutritional habits [9].

Orlistat is a potent, irreversible inhibitor of carboxylester lipase. This medication inhibits the digestion of dietary triglycerides and decreases the absorption of lipids [10].

The aims of this study were to determine the effect of combined orlistat and conventional hypo caloric diet compared to diet alone in overweight and obese women with PCOS.

Materials and methods

This was a randomized double-blind, placebo-controlled clinical trial. We recruited 100 patients from our clinic at Arash Hospital between May 2010 and May 2012. After obtaining informed consents, we used the randomization table method to divide the patients into two groups. All patients were diagnosed with PCOS according to Rotterdam Criteria (2004). Patients' primary complaints included abnormal menses (oligomenorrhea and menometrorrhagia). All patients were of reproductive age (19–38 years) and had a body mass index (BMI) > 25. Study participants had no histories of taking hormonal medications in last six months, no current dietary modifications or dietary modifications for the preceding six months prior to study entry. The exclusion criteria were as follows: a history of cholestasis, liver disease, renal disease, malabsorbtion, or hypothyroidism. All patients received a hypocaloric diet that consisted of 55 % carbohydrates, 30 % fat, and 15 % protein. Each serving of this diet provided approximately 1,200–1,800 kilocalories per day according to each individual's primary BMI. This is monounsaturated fatty acid (MUFA) diet—one of the diet protocols which is used in PCOS [11–13]. The patients had normal physical activity and were encouraged to walk for 30 min daily. Participants completed weekly exercise diaries to monitor for

Electronic supplementary material The online version of this article (doi:10.1007/s12020-014-0426-4) contains supplementary material, which is available to authorized users.

A. Moini · M. Kanani · L. Kashani · R. Hosseini (✉)
Department of Gynecology and Obstetrics, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran
e-mail: rayh_h@yahoo.com

A. Moini
Department of Endocrinology and Female Infertility, Royan Institute ACECR, Tehran, Iran

L. Hosseini
Research Development Center, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran

compliance. The consistency of exercise was 77 % in the control group and 74.8 % in the intervention group.

The intervention group received orlistat (120 mg) three times per day. The control group received a placebo. Both the placebo and orlistat were manufactured by Aburaihan Pharmaceutical Company and were identical in shape. The duration of treatment was 3 months. A member of the study team who was blinded to both groups visited each participant monthly.

Weight, BMI [weight (kg)/height (m^2)], and waist circumference were measured at the beginning and at the end of the three-month period. Insulin (2.0–25.0 μu/ml) and total testosterone during the follicular phase (0.14–0.9 ng/ml) were measured using ELISA (Monobid, USA). Fasting glucose (≤100 mg/dl), triglycerides (≤150 mg/dl), and high density lipoprotein (HDL > 40 mg/dl) were determined by photometry (Parsazmoon, Iran). Our findings showed an inter-assay variation of <5 % and intra-assay variation of <8 % for testosterone and insulin. We used the homeostatic model assessment of insulin resistance (HOMA-IR) to evaluate insulin resistance based on the following formula: fasting plasma glucose (mg/dl) × fasting plasma insulin (μU/ml) divided by 405.

All participants were advised to use a non-hormonal contraception method. The effect of treatment was evaluated by comparing the changes in variables before and after treatment in both groups.

We used a mixed design (between and within groups) analysis of variance (ANOVA) in order to provide both inter- and intra-group comparisons. Relationships between different values of the variables were subsequently explored using simple comparison between the obtained measurement and baseline by the *t* test or Mann–Whitney test according to the variables' distributions. We considered a *p* value <0.05 as significant. The analysis was performed using the Statistical Package for Social Sciences (SPSS) version 16 (SPSS Inc., Chicago, IL, USA).

Results

In the intervention ($n = 50$) and control groups ($n = 50$), the same numbers of participants completed the study ($n = 43$ for both groups). Participants' mean age was 27.42 ± 3.31 years in the control group and 26.80 ± 5.16 years in the intervention group. Participants were excluded from the study for the following reasons: lack of compliance for follow-up visits (4 in the control group and 3 in the intervention group); participants expressed concerns about treatment/side effects (one in the control group and 2 in the intervention group); the presence of medical conditions (one in the intervention group); and use of different medical treatments (2 in the control group and one in the intervention group).

A comparison between before and after treatment showed a significant decline in BMI ($p < 0.01$) and testosterone level ($p < 0.01$) in the intervention group compared with BMI ($p = 0.43$) and testosterone level ($p = 0.39$) in the control group. Although participants had a significant mean weight loss in the control group from 80.91 kg at the beginning of the study to 79.15 kg after treatment ($p = 0.01$), the reduction in BMI was not significant. There was a 6.37 % weight loss in the intervention group and 2.27 % weight loss in the control group. After 3 months of treatment, the BMI was 27.16 ± 1.93 in the intervention group and 28.50 ± 1.9 in the control group, which its difference was significant ($p < 0.001$). The changes in parameters are shown in Table 1.

The control group comprised 31 individuals with oligomenorrhea, 10 with menometrorrhagia, and 2 with normal menses. In the intervention group, there were 28 patients with oligomenorrhea, 12 with menometrorrhagia, and 3 who had normal menses. After treatment, there were a total of 4 individuals with normal menses in the control group and 6 in the intervention group, which was not significantly different both before and after treatment and between the two groups.

The mean triglyceride levels were 103.61 ± 13.2 mg/dL for the intervention group and 159.97 ± 11.93 mg/dL for the control group, which showed a substantial decrease in the intervention group ($p < 0.01$). We observed the same decrease in plasma low-density lipoprotein (LDL) levels with a mean of 71.18 ± 2.34 mg/dL in the intervention group and 102.83 ± 6.90 mg/dL in the control group ($p < 0.01$). Additionally, an increase in HDL level in the intervention group (54.13 ± 2.32 mg/dL) was observed compared to the control group (49.23 ± 1.47 mg/dL; $p < 0.01$).

Even after controlling for the effect of weight loss by regression analysis, it was noted that orlistat significantly decreased LDL and triglyceride levels, increased HDL levels, and showed no significant changes in insulin and fasting glucose levels. Also inter- and intra-group comparisons of HOMA-IR showed no significant changes in the control and intervention groups (Table 1).

Approximately 50 % of intervention group patients complained of adverse effects that included an urgent need to go to the bathroom (54 %), oily spotting in undergarments (30 %), oily or fatty stools (22 %), and headaches (3 %). In the control group 13 (22 %) patients reported the following side effects of headaches (2 patients), dizziness (4 patients), and defecation problems (diarrhea or constipation in 7 patients). There was no case of drug discontinuation due to any reported adverse effects.

Discussion

It has been shown that treatment with orlistat is effective for weight loss in obese patients. Mild weight loss (5 % of

Table 1 Comparison between characteristics of two groups before and after treatment

Parameters	Treatment group Mean ± SD			Control group Mean ± SD			Comparison between two groups before	Comparison between two groups after
	Before	After	*p*	Before	After	*p*	*p*	*p*
Weight (kg)	81.5 ± 4.04	76.25 ± 4.3	<0.01	80.91 ± 4.23	79.15 ± 4.51	0.01	0.14	<0.01
BMI (kg/m^2)	29.01 ± 2.09	27.16 ± 1.93	<0.01	28.60 ± 4.2	28.57 ± 1.90	0.43	0.54	<0.01
WHR (cm)	0.88 ± 0.04	0.76 ± 0.03	<0.01	0.87 ± 0.03	0.86 ± 0.03	0.68	0.78	<0.01
Testosterone (ng/ml)	83.46 ± 5.08	63.95 ± 1.63	<0.01	82.56 ± 4.85	81.60 ± 4.64	0.39	0.39	0.01
Fasting insulin (μu/ml)	17.24 ± 6.49	17.20 ± 6.72	0.21	17.49 ± 6.83	17.34 ± 7.27	0.52	0.39	0.97
Fasting blood glucose (mg/dl)	107.61 ± 4.44	107.05 ± 4.24	0.06	106.70 ± 4.40	106.35 ± 4.24	0.16	0.85	0.62
HOMA-IR	3.46 ± 1.99	3.43 ± 1.11	0.43	3.43 ± 1.70	3.41 ± 1.42	0.61	0.08	0.21
Triglyceride (mg/dl)	157.09 ± 11.70	128.34 ± 16.52	<0.01	159.97.02 ± 11.52	158.98 ± 11.93	<0.01	0.45	<0.01
LDL (mg/dl)	96.47 ± 5.11	71.18 ± 2.34	<0.01	102.83 ± 6.90	99.63 ± 5.80	<0.01	0.25	<0.01
HDL (mg/dl)	48.75 ± 2.37	54.13 ± 2.32	<0.01	48.30 ± 2.36	49.23 ± 1.47	<0.01	0.08	<0.01

initial body weight) has been shown to increase the frequency of ovulation and fecundity and improve testosterone and lipid profiles in women with PCOS [3–7]. In this study we aimed to compare the effect of orlistat, an anti-obesity drug, in combination with conventional hypocaloric diet to diet alone in terms of weight loss. We sought to determine the hormonal and metabolic consequences in PCOS women.

Our data demonstrated that orlistat combined with a mild low-calorie diet was associated with a reduction in body weight in obese PCOS patients. Our finding (6.3 % weight loss) is consistent with Heymsfield et al. study (6.8 % weight loss) in 1 year treatment [14] and Jayagopal et al. (4.69 % in 3 months) [15]. Although in the control group we observed a reduction in weight, the reduction in BMI was not significant. Of note, BMI changes take longer than weight changes. Following a restricted diet and an exercise program for an extended period of time is difficult for many obese patients. According to a review article by Bray et al., although diet and lifestyle improvement are the first lines of any weight-loss strategy in obese patients, in many cases additional interventions may be necessary [16].

In the current study, the intervention group showed a significant reduction in testosterone levels which was consistent with other reports for PCOS patients [17, 18]. The androgen excess has two main pathways in PCOS: First, increased level of LH and Insulin stimulated P450c17 and its androgen production. Second, the level of sex hormone binding globulin (SHBG) is lower in PCOS patients [19]. In our study, the testosterone levels decreased without any major changes in insulin levels, which might be attributed to the changes SHBG levels or a modification in secretion pattern following treatment.

Both groups experienced significant decreases in lipid profiles, which were consistent with the results of a study by Ghandi on PCOS women [20]. An increase in HDL level was also observed. However, these changes were more significant in the intervention group.

Cho et al. reported an effect of orlistat on insulin resistance in PCOS women [21]; however, in the current study, there was no substantial effect of orlistat on glucose and insulin levels and also HOMA-IR. Sahin et al. [22]. and Jayagopal et al. [15] have also reported the same results in non-diabetic obese women. Of note, the balance in glucose profiles is related to constant weight loss and reduction of blood lipids which is expected during long-term follow-up. The difference among findings may be attributed to a longer follow-up, for example, in Heymsfield et al. study (one-year treatment) [14] or larger sample size in Jacob et al. study [23]. Also in the last study, the cases had diabetes and the duration of treatment was different in cases.

The same conclusion can be applied for the current study's control group as they showed improvements in lipid profile and weight; however, BMI and glucose/insulin levels failed to be influenced by the low-caloric diet during this short-term follow-up. Possibly, long-term treatment might change these findings as has been shown in a study by Mehrabani et al. [24] on PCOS obesity.

If the treatment period were longer, it was possible that additional adverse effects might disturb the patients as has been reported by Johansson et al. [25].

According to this study and those by Ghandi et al. [20], Diaz and Folgueras [26], and Smith et al. [27], it seems that

orlistat is a reasonable drug for obese patients diagnosed with PCOS and those without PCOS. On the other hand, adverse effects and the need for long-term treatment limit its use.

This study has a relatively appropriate sample size, a PCOS control group, and a randomized double-blind design, which can reduce the bias risk compare with previous studies. However, more studies that have a longer duration of treatment are needed to evaluate the effects of this drug.

Acknowledgments This study was financially supported by Tehran University of Medical Sciences. We express our appreciation to Fariborz Sadeghi Shahrestani for his kind cooperation.

Conflict of interest The authors report no conflict of interest.

References

1. S. Franks, Polycystic ovary syndrome. N. Engl. J. Med. **13**, 853–861 (1995)
2. S.E. Kedikova, M.M. Sirakov, M.V. Boyadzhieva, Leptin levels and adipose tissue percentage in adolescents with polycystico vary syndrome. Gynecol. Endocrinol. **29**, 384–387 (2013)
3. R.S. Legro, Obesity and PCOS: implications for diagnosis and treatment. Semin. Reprod. Med. **30**, 496–506 (2012)
4. A.K. Schröder, S. Tauchert, O. Ortmann, K. Diedrich, J.M. Weiss, Insulin resistance in patients with polycystic ovary syndrome. Ann. Med. **36**, 426–439 (2004)
5. R.S. Legro, A.R. Kunselman, W.C. Dodson, A. Dunaif, Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J. Clin. Endocrinol. Metab. **84**, 165–169 (1999)
6. A.B. Motta, The role of obesity in the development of polycystic ovary syndrome. Current Pharm. Des. **18**, 2482–2491 (2012)
7. R. Pasquali, A. Gambineri, U. Pagotto, The impact of obesity on reproduction in women with polycystic ovary syndrome. BJOG **113**, 1148–1159 (2006)
8. H.F. Escobar-Morreale, J.L. San Millán, Abdominal adiposity and the polycystic ovary syndrome. Trends Endocrinol. Metab. **18**, 266–272 (2007)
9. P. Ravn, A.G. Haugen, D. Glintborg, Overweight in polycystic ovary syndrome. An update on evidence based advice on diet, exercise and metformin use for weight loss. Minerva Endocrinol. **38**, 59–76 (2013)
10. M.M. Huber-Buchholz, D.G. Carey, R.J. Norman, Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J. Clin. Endocrinol. Metab. **84**, 1470–1474 (1999)
11. M. Parillo, A.A. Rivellese, A.V. Ciardullo, B. Capaldo, A. Giacco, S. Genovese et al., A highmonounsaturated-fat/low-carbohydrate diet improves peripheral insulin sensitivity in non-insulindependent diabetic patients. Metabolism **41**, 1373–1378 (1992)
12. A. Garg, A. Bonanome, S.M. Grundy, Z. Zhang, R.H. Unger, Comparison of a high-carbohydrate diet with a high-monounsaturated-fat diet in patients with non-insulin-dependent diabetes mellitus. N. Engl. J. Med. **319**, 829–834 (1988)
13. C.C. Douglas, B.A. Gower, B.E. Darnell, F. Ovalle, R.A. Oster, R. Azziz, Role of diet in the treatment of polycystic ovary syndrome. Fertil. Steril. **85**, 679–688 (2006)
14. S.B. Heymsfield, K.R. Segal, J. Hauptman, C.P. Lucas, M.N. Boldrin, A. Rissanen, J.P.H. Wilding, L. Sjöström, Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. Arch. Intern. Med. **160**, 1321–1326 (2000)
15. V. Jayagopal, E.S. Kilpatrick, S. Holding, P.E. Jennings, S.L. Atkin, Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. J. Clin. Endocrinol. Metab. **90**, 729–733 (2005)
16. G. Bray, M. Look, D. Ryan, Treatment of the obese patient in primary care: targeting and meeting goals and expectations. Postgrad. Med. **125**, 67–77 (2013)
17. D. Panidis, K. Tziomalos, E. Papadakis, P. Chatzis, E.A. Kandaraki, E.A. Tsourdi, I. Katsikis, The role of orlistat combined with lifestyle changes in the management of overweight and obese patients with polycystic ovary syndrome. Clin. Endocrinol. **80**, 432–438 (2014)
18. M. Metwally, S. Amer, T.C. Li, W.L. Ledger, An RCT of metformin versus orlistatfor the management of obese anovulatory women. Hum. Reprod. **24**, 966–975 (2009)
19. R. Homburg, Androgen circle of polycystic ovary syndrome. Hum. Reprod. **24**, 1548–1555 (2009)
20. S. Ghandi, A. Aflatoonian, N. Tabibnejad, M.H. SojoodiMoghaddam, The effects of metformin or orlistat on obese women with polycystic ovary syndrome: a prospective randomized open-label study. J. Assist. Reprod. Genet. **28**, 591–596 (2011)
21. L.W. Cho, E.S. Kilpatrick, B.G. Keevil, A.M. Coady, S.L. Atkin, Effect of metformin, orlistat and pioglitazone treatment on mean insulin resistance and its biological variability in polycystic ovary syndrome. Clin. Endocrinol. **70**, 233–237 (2009)
22. M. Sahin, N. Tanaci, M. Yucel, N.B. Tutuncu, N. Guvener, The effect of single-dose Orlistat on postprandial serum glucose, insulin and glucagon-like peptide-1 levels in nondiabetic obese patients. Clin. Endocrinol. **67**, 346–350 (2007)
23. S. Jacob, M. Rabbia, M.K. Meier, J. Hauptman, Orlistat 120 mg improves glycaemic control in type 2 diabetic patients with or without concurrent weight loss. Diabetes Obes. Metab. **11**, 361–371 (2009)
24. H.H. Mehrabani, S. Salehpour, Z. Amiri, S.J. Farahani, B.J. Meyer, F. Tahbaz, Beneficial effects of a high-protein, low-glycemic-load hypocaloric diet in overweight and obese women with polycystic ovary syndrome: a randomized controlled intervention study. J. Am. Coll. Nutr. **31**, 117–125 (2012)
25. K. Johansson, K. Neovius, S.M. DeSantis, S. Rössner, M. Neovius, Discontinuation due to adverse events in randomized trials of orlistat, sibutramine and rimonabant: a meta-analysis. Obes. Rev. **10**, 564–575 (2009)
26. E.G. Diaz, T.M. Folgueras, Systematic review of the clinical efficacy of sibutramine and orlistat in weigth loss, quality of life and its adverse effects in obese adolescents. Nutr. Hosp. **26**, 451–457 (2011)
27. S.R. Smith, K.S. Stenlof, F.L. Greenway, J. McHutchison, S.M. Schwartz, V.B. Dev, E.S. Berk, R. Kapikian, Orlistat 60 mg reduces visceral adipose tissue: a 24-week randomized, placebo-controlled, multicenter trial. Obesity **19**, 1796–1803 (2011)