Effects of orlistat on serum androgen levels among iranian obese women with polycystic ovarian syndrome

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ABSTRACT

Introduction: Polycystic ovary syndrome is one of the most common endocrinopathies in young women, and it affects 6% to 8% of women in reproductive age. Hyperandrogenism is the hallmark of polycystic ovary syndrome. The aim of the present study was to evaluate the effects of orlistat on weight loss and serum androgen levels among Iranian women with polycystic ovarian syndrome.

Methods: The present study was carried out in the clinic of Infertility and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Thirty-two patients with polycystic ovary syndrome were randomly enrolled. We measured serum androgens (Testosterone, 17α-hydroxyprogesterone, dehydroepiandrosterone and sex hormone-binding globulin) before and after 12 weeks of treatment with orlistat. We used the Rotterdam Criteria for all patients and transvaginal sonography was performed.

Results: The mean age of patients was 27.75±6.22 and the mean body mass index was 32.69±0.94 kg/m². Comparing with baseline, treatment with orlistat resulted in a significant reduction in weight, BMI, and waist circumference (p=0.001). We also found a remarkable reduction in total testosterone levels (p<0.001). Treatment improved the sex hormone-binding globulin plasma levels, but the improvement was not statistically significant. There was no reduction in other androgen levels.

Conclusion: This study showed a significant reduction of weight and total testosterone level - the most important androgen in polycystic ovary syndrome - after 12 weeks of treatment with orlistat. Therefore, it seems that a short course of orlistat can be useful in the management of patients with polycystic ovary syndrome.

Keywords: Polycystic ovary syndrome, orlistat, androgen, weight loss, Iran

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies among young women (Knochenhauer et al., 1998). Chronic anovulation, clinical and laboratory evidence of hyperandrogenism, and ultrasound detection of micro polycystic ovaries (Azziz et al., 2009) characterize it. It is a heterogeneous disorder of unclear etiopathogenesis but there is evidence of the participation of a genetic component (Xita et al., 2002). Stein and Leventhal (Zárate-Treviño et al., 2014) are often credited with publishing the first paper describing PCOS, in 1935. Since their description of women with ovarian enlargement and absence of menses more than 80 years ago, PCOS has garnered considerable attention and might be the most common endocrine disorder, affecting up to 15% of all women in reproductive age, depending on the diagnostic criteria used (Vignesh & Mohan, 2007).

Hyperandrogenism is the hallmark of PCOS. Clinically, we may see hirsutism, acne, androgenic alopecia, and signs of virilization. Laboratory examination reveals increased androgen levels (Azziz et al., 2009), which are associated with inhibition of follicle development, anovulation, menstrual changes, and microcysts in the ovaries (Adams et al., 1986; Lin et al., 2013).

Hyperandrogenicity in connection with over nutrition has been shown to lead to central, ‘visceral’ obesity among PCOS patients (Björntorp, 1988; Kissebah et al., 1982; Vague, 1956), with an increase in circulating free fatty acids, and a reduction in insulin sensitivity and hepatic sex-hormone-binding-globulin (SHBG) production (Björntorp, 1988; Kissebah et al., 1982). Leptin, adiponectin, ghrelin, homocysteine, insulin resistance and other biochemical factors may play a relevant role in some enigmatic reproductive disturbances such as PCOS (Salehpour et al., 2008).

Metabolic disturbances are well-recognized clinical features of this syndrome. Especially, dyslipidemia is a very common metabolic abnormality in women with PCOS, with a prevalence of up to 70% (Legro et al., 2001). Insulin resistance is a key pathophysiological component of PCOS, thus dyslipidemia in women with PCOS may be consistent with those found in an insulin resistant state (Kim & Choi, 2013). In addition, a decrease in HDL-C and increase in TG levels are well-known lipid profile characteristics in women with PCOS (Bruzell & Ayyob, 2003; Dejager et al., 2001; Yilmaz et al., 2005).

Whatever the etiology of obesity, found in 50% of women with PCOS, weight loss is frequently associated with correction of the hormonal abnormalities in PCOS and the reestablishment of regular ovulation (Kiddy et al., 1992; Ravn et al., 2013). Weight loss is considered a first-line treatment in overweight women with PCOS (Ravn et al., 2013). Lifestyle changes improve the lipid profile in PCOS patients, and may be used as a first-line management procedure for ovulation induction in these patients. Unfortunately, long-term success of lifestyle modifications is not often achieved. Consequently, there is an urgent need to develop and validate appropriate pharmacological interventions to improve metabolic function in women with PCOS. Bozdag & Yildiz (2013) studied the lifestyle change interventions and medical approaches in the context of the management of metabolic alterations in PCOS. The authors concluded that lifestyle intervention improves body composition, hyperandrogenism and insulin resistance in women with PCOS, there was no evidence of effect on improving glucose tolerance or lipid profile.

The use of pharmacological agents as adjunctive therapy for weight management is universally recommended by the most relevant clinical guidelines and consensus documents (Wadden et al., 2005; National Institutes of Health, 1998; Coutinho & Cabral, 2000). Orlistat is an anti-obesity drug, which promotes weight loss by decreasing fat absorption from the intestine lumen by about 30% (Dixon, 2006; Padwal & Majumdar, 2007). Because weight loss is
associated with improvement in ovarian function in PCOS women, it seems that orlistat may increase ovulation rate as well (Ghandi et al., 2011). Orlistat is currently the only lipase inhibitor approved for weight loss, and it is a potent inhibitor of pancreatic and gastric lipases, acting locally in the gut lumen with minimal absorption.

Orlistat, combined with lifestyle changes, induces substantial weight loss in women with PCOS, resulting in improvements in insulin resistance, hyperandrogenemia and cardiovascular risk factors (Panidis et al., 2014; Vosnakis et al., 2013). Vosnakis et al. (2013) demonstrated that in overweight and obese women with PCOS, orlistat administration (120 mg, 3 times per day) for 24 weeks, combined with diet and physical exercise, for 24 weeks, resulted in significant weight loss, improvement of hyperandrogenism and insulin sensitivity, and increased serum AMH levels. Ghandi et al. (2011) in comparing the effects of metformin or orlistat on hormonal, lipid profile and ovulation status in obese women with polycystic ovary syndrome, found that treatment with either drug caused a significant decline in body weight, BMI (Body Mass Index), and waist circumference, and the degree of decline in both groups was the same. Patients who were treated with orlistat, showed a significant reduction in total testosterone and serum lipid.

The present study was designed to further investigate the effects of treatment with orlistat, for a period of 12 weeks, on anthropometric features and serum androgen levels in women with PCOS.

MATERIALS AND METHODS

Patients

The present study was approved by the ethics committee of Infertility and Reproductive Health Research Center of the Taleghani Hospital, and it approved by the School of Medicine of the Shahid Beheshti University of Medical Sciences, Tehran, Iran. Written informed consent was obtained from all patients before enrolling in the study. The study followed the principles of the Declaration of Helsinki.

The patients were recruited from the gynecology outpatient clinic, between December 2012 and November 2013. The study included thirty-two women who met all of the following conditions: diagnosed to have PCOS, aged between 19 and 44 years, and BMI ≥25kg/m². The diagnosis of PCOS was made according to the revised 2003 European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) Rotterdam Criteria (Rotterdam ES/REHRE/ASRM-sponsored PCOS consensus workshop Group, 2004), with the presence of at least two of the following three features after exclusion of other etiologies: oligo-or anovulation, clinical and/or biochemical hyperandrogenism and ultrasound finding of polycystic ovaries (presence of 12 or more follicles in each ovary measuring 2-9 millimeter in diameter, and/or increased ovarian volume (>10ml). The sonography device used was the Esate MyLab Xvision 70 (Esaote, Italy).

Exclusion criteria were: non classical form of 21-hydroxylase deficiency, hyperprolactinemia, Cushing syndrome, androgen excess hormone tumors, orlistat complications during consumption and any sensitivity, chronic malabsorption disease, cholesterol, renal or hepatic impairment, presence of impaired fasting glycaemia, untreated hypothyroidism, current pregnancy or on breastfeeding, having any disease other than PCOS, any history of medication in the past 6 months (like metformin, amiodarone, cyclosporine, warfarin) and severe Vit-D deficiency.

Study Design

The patients’ visits were scheduled according to menstrual cycle, during the follicular phase, and for those with anovulatory cycles, in the amenorrhea phase. At the initial evaluation (baseline), the basal metabolic rate (in kcal/d) of all women was calculated and adjusted for moderate daily physical activity as follow: in women 18-30 years of age: (0.0621 × weight in kg + 2.0357) × 240 × 1.3 and, in women >31 years of age: (0.0342 × weight in kg + 3.5377) × 240 × 1.3.

A dose of 120mg orlistat was taken three times daily and the dose remained constant throughout the study period.

The subjects were weighed in kilograms using a digital scale, wearing light clothes and no shoes, at 9:00 AM (after an overnight fast), at baseline and at week 12 after treatment onset. Their height was measured in centimeters using a wall-mounted measuring tape.

BMI was calculated using this formula: weight (kg)/height (m²). Waist and hip circumferences were measured in duplicate in the supine position, and their ratio (WHR) was calculated.

Blood samples were collected, and the basal serum levels of FSH, LH, PRL, total and free testosterone levels, dehydroepiandrosterone sulfate (DHEAS), 17α-hydroxyprogesterone (17α-OHP) and sex hormone-binding globulin (SHBG) were measured. Clinical and biochemical assessments were performed at random and at the end of the 3-months treatment period.

Laboratory Measurements

After 12 hours of overnight fasting, a blood sample was drawn from the antecubital region and into vacutainer tubes. The sample was maintained at 4°C for ≤2 hours before centrifugation. Serum aliquots were frozen at -80°C for subsequent analyses. Fasting serum glucose, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured using the enzymatic colorimetric method (PishtazTeb Inc., Tehran, Iran), by a Hitachi auto-analyzer (Tokyo, Japan). In all the biochemical analyses, the intra-assay coefficients of variation (CVs) were less than 2.0%.

Serum thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH) and luteinizing hormone (LH), as well as prolactin hormone (PRL) were measured by a Micro plate Immunoenzymometric assay (IEMA/ELISA), using Monobind Inc. kits (Lake Forest, CA, USA).

We used the micro plate immunoenzymometric assay for determining 17α-OHP, total and free testosterone, as well as DHEAS using Accu-Bind kits, Monobind Inc. (Lake Forest, CA, USA).

SHBG was determined in an Enzyme immunoassay (ELISA) using IBL INTERNATIONAL GMBH kits (Hamburg, Germany).

Q Sure™ [Quality Control Sera, MULTI LIGAND CONTROL-TRI LEVEL] was used as a quality control material to assist in the assessment of precision in the clinical laboratory, from Monobind Inc. (Lake Forest, CA, USA).

Statistical analysis

For statistical analysis, we used the SPSS for windows version 16.0 (SPSS Inc., Chicago, IL, USA) software package. The categorical data was studied using frequency analysis. Clinical characteristics were compared by parametric or non-parametric tests for independent samples, as appropriate. The data is presented as percentage, mean±SD, or median (range). In this study, p<0.05 was considered to indicate statistical significance.

RESULTS

The present study included 32 women with PCOS. The mean age was 27.75±6.22 and the mean body mass index
was 32.69±0.94 kg/m². All subjects completed the three-month study. Two patients showed cramping and oily stool during the first 2 weeks of treatment but it was not necessary to stop treatment or reduce the drug dosage. Demographic and clinical characteristics of the PCOS patients are presented in Table 1.

### Table 1. Baseline characteristics in PCOS patients

| Characteristic          | Value (n=32) |
|-------------------------|-------------|
| Age (Years) (Mean)      | 27.75±6.22  |
| History of infertility (Number, Percentage) | 21(65%) |
| Weight (Kilogram) (Mean) | 83.96±2.4   |
| Height (Centimeter) (Mean) | 161±1.20    |
| BMI (Kilogram) (Mean)   | 32.69±0.94  |
| Waist circumference (Centimeter) (Mean) | 114.15±10.06 |
| TSH (mIU/L) (Mean)      | 3.39±0.25   |
| PRL (ng/mL) (Mean)      | 8.8 ±0.59   |

Compared with baseline, treatment with orlistat (Table 2) resulted in a significant reduction in weight, BMI, and waist circumference. We also found a remarkable reduction in total testosterone levels (p<0.05). There was no reduction in other androgen levels.

In addition, orlistat treatment improved the metabolic profile and SHBG plasma levels, but the difference was not significant. Lipid profile changes after orlistat included significant increase in HDL levels. Conversely, orlistat had no effect on other lipid profiles.

**DISCUSSION**

It has been shown that treatment with orlistat is effective for amelioration of the PCOS hormonal and metabolic consequences for women (Metwally et al., 2009; Lord et al., 2003; De Sloover Koch & Ernst, 2001). Therefore, we studied the effect of orlistat, as an anti-obesity drug, on hormonal and androgen level statuses in obese PCOS patients. This study is the second study among Iranian patients, which assessed the effects of this drug on androgen levels among PCOS patients. The first study was carried out by Ghandi et al. (2011).

In the present study, treatment with orlistat reduced serum testosterone levels. This finding is consistent with previous studies, in which orlistat therapy decreased serum testosterone levels (Panidis et al., 2014; Vosnakis et al., 2013; Lord et al., 2003; Sharpe & Franks, 2002). Nevertheless, in some studies orlistat reduced weight and waist circumference but did not affect testosterone levels (Agarwal et al., 2010).

In the present study, treatment with orlistat caused a significant reduction in body weight and BMI. Our study results were in agreement with those from the Panidis et al. (2014) study. They reported that orlistat combined with lifestyle changes induces substantial weight loss in women with PCOS, resulting in improvements in hyperandrogenemia. Orlistat is a weight-loss drug with minimal systemic absorption (Padwal & Majumdar, 2007), and therefore any effect of this drug is a result of weight loss and not a direct effect on ovaries.

The treatment with orlistat in this study resulted in a significant increase in HDL, but no significant reduction in serum cholesterol, triglyceride and LDL, so it is not in agreement with other studies in which orlistat improved other lipoproteins in the lipid profile (Lord et al., 2003; Metwally et al., 2009). In a study by Ghandi et al. (2011), treatment with orlistat resulted in a significant decline in total serum cholesterol and triglycerides.

Weight reduction in PCOS has been reported to improve hyperinsulinemia (Huber-Buchholz et al., 1999; Andersen et al., 1995; Hamilton-Fairley et al., 1993), and reduce serum LH levels (Poretsky et al., 1999). Moreover, orlistat affects insulin levels indirectly through weight reduction. In the present study, orlistat had no statistically significant effect on fasting insulin and LH levels. It seems that longer treatment with orlistat is needed to reach a significant reduction in serum LH level.

PCOS is associated with low-grade chronic inflammation, mainly attributable to the build-up of visceral fat, although an insulin resistance effect cannot be excluded (Repaci et al., 2011). The impact of hyperandrogenemia can be related to the influence of androgens on adipose tissue development and distribution. In addition, through the impact on the regulation of the synthesis and secretion of androgens in the ovary and in the adrenal gland, the state of low-grade inflammation also seems able to contribute to maintain the syndrome (Duleba, 2012). Orlistat consistently improves lipid profile and markers of systemic inflammation (Duleba, 2012).

### Table 2. Comparison of patients’ characteristics at the baseline and after 3-months of treatment with orlistat

| Parameters                  | Baseline | After treatment | p-value* |
|-----------------------------|----------|----------------|----------|
| BMI (kg/m²) (Mean)          | 32.69±0.94 | 30.62±0.78      | <0.001   |
| Waist (cm) (Mean)           | 114.15±10.06 | 111.05±11.67    | <0.001   |
| Testosterone (ng/ml) (Mean) | 0.80±0.23  | 0.63±0.22       | <0.001   |
| 17α-OH Progesterone (ng/ml) (Mean) | 1.13±0.11 | 1.00±1.1        | NS       |
| DHEA-S (µg/ml) (Mean)       | 2.17±0.29  | 2.12±0.29       | NS       |
| SHBG (nmol/l) (Mean)        | 24.77±3.3  | 30.59±6.5       | NS       |
| LH (mIU/ml) (Mean)          | 12.94±1.7  | 11.36±1.06      | NS       |
| FSH (mIU/ml) (Mean)         | 5.53±0.51  | 8.77±3.39       | NS       |

NS: Not Significant
In our study, Orlistat showed a significant HDL increasing effect. These increasing levels of HDL might be attributable to a strong protection against cardiovascular disease in the future for PCOS patients. A shortcoming of the present study was its relatively low number of participants, which might have led to some of the relations not reaching a significance level. Further studies with higher number of samples are recommended.

In conclusion, this study showed a significant reduction in weight and total testosterone level, as the most important androgen, in polycystic ovary syndrome patients after 12 weeks of treatment with Orlistat. Therefore, it seems that a short course of Orlistat can be useful in the management of patients with polycystic ovary syndrome.

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Conflict of interest

None of authors has any conflict of interest with the subject matter of this manuscript.

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