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ORIGINAL ARTICLE

Effect of hypocaloric diet plus sibutramine treatment on hormonal and metabolic features in overweight and obese women with polycystic ovary syndrome: a randomized, 24-week study

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Objective: To examine the effect of hypocaloric diet plus sibutramine on body composition, hormonal and metabolic parameters in overweight and obese patients with polycystic ovary syndrome (PCOS).
Design: Open-label, randomized study at an outpatient clinic.
Patients: A total of 59 overweight and obese (18–39 years old) women with PCOS.
Measurements: All patients were placed in a hypocaloric diet plus sibutramine (10 mg per day) for the first month and then on a hypocaloric diet plus sibutramine (10 mg per day, group S) or hypocaloric diet only (group D) for the subsequent 6 months. Body composition, hormonal and metabolic features and insulin sensitivity (oral glucose tolerance test, OGTT) were evaluated at baseline and at 3 and 6 months of treatment.
Results: Body weight reduced in both groups but the reduction was greater with sibutramine (-15.4 ± 1.1 vs -11.1 ± 1.9% in groups S and D, respectively, $P<0.05$). At 6 months, a greater percent of patients lost more than 10% of initial body weight in group S than D (81 vs 52.9%). In both groups, all women with abnormal OGTT at baseline presented normal glucose tolerance after 6 months. Free androgen index (FAI), glucose area under the curve and fasting triglyceride (TG) concentration were reduced after 6 months in group S only ($P<0.05$). No changes in cardiovascular risk factors, prolactin and hepatic enzymes levels were observed in both groups.
Conclusion: A hypocaloric diet and a diet plus sibutramine both result in significant weight loss in overweight and obese women with PCOS. Patients who received sibutramine showed a greater weight loss and improvement in hyperandrogenemia and insulin sensitivity after 6 months of treatment. The amelioration of insulin resistance in this group could not be totally explained by weight loss. Total testosterone, FAI and TG levels reduction could be a possible mechanism. Finally, sibutramine increased compliance to diet and it was well tolerated from these patients.
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Keywords: sibutramine; hyperandrogenemia; insulin sensitivity; polycystic ovary syndrome

Introduction

The polycystic ovary syndrome (PCOS) is one of the most common hormonal disorders of women of reproductive age. As a syndrome it has multiple components, such as reproductive (chronic anovulation and infertility), metabolic and cardiovascular abnormalities. Although lean women present PCOS, obesity is one of the main manifestations of this syndrome. PCOS prevalence is 5–7% in women of

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reproductive age, although a cross-sectional study in Greece reported prevalence of 9% among women with hyperandrogenism and prolonged menstrual cycles.[1] Androgen excess and insulin resistance (IR) underline much of the clinical and metabolic features of the syndrome. The 2003 Rotterdam consensus workshop revised the PCOS diagnostic criteria suggesting that it is a syndrome of ovarian dysfunction along with the cardinal features hyperandrogenism and polycystic ovary morphology.[2]

Recent evidence suggests that PCOS patients have a substantial risk for the development of metabolic and cardiovascular abnormalities similar to those presented in the metabolic syndrome.[3] Therefore, PCOS has been characterized as a sex-specific form of the metabolic syndrome and the term 'syndrome XX' has been suggested.[4] Many features of the metabolic syndrome are common in PCOS, which represents a unique model to investigate the association between obesity and female reproductive function.

Obesity, particularly of the abdominal type, is presented in approximately half of the women with PCOS, although studies show that this rate vary from 30 to 75% and from 10 to 38% in the Mediterranean area.[3,5] Several studies have demonstrated that obesity in PCOS women enhances the clinical and metabolic abnormalities of the syndrome. Indeed, obese women with PCOS have more profound IR or type 2 diabetes mellitus,[6–8] dyslipidemia and risk of cardiovascular disease,[9–12] and greater level of androgens due to low levels of sex hormone-binding globulin (SHBG).[13]

A modest weight loss (>5% of initial body weight) improves ovulation frequency and conception, reduces miscarriage, hyperlipidemia, hypertension, hyperglycemia and IR in women with PCOS.[14–21] There are only a few studies in the literature on the effect of antiobesity drug administration on metabolic and other parameters in overweight and obese women with PCOS. Previous studies with orlistat and metformin showed a significant reduction in body weight, androgen levels and metabolic cardiovascular risk factors in PCOS women.[22,23] To our best knowledge, the effect of sibutramine, a serotonin and norepinephrine reuptake inhibitor (SNRI) approved as antiobesity drug, has been examined in only one study with obese PCOS women.[24]

Given this lack of information, the aim of the present study was to investigate any additional effect of sibutramine combined with a hypocaloric diet on body composition, hormonal and lipids parameters, and IR in overweight and obese women with PCOS.

Patients and methods

Subjects

Outpatients, premenopausal, nonpregnant, nonlactating, overweight and obese women (body mass index, BMI>27), 18 years of age and older with PCOS were recruited for this study. The diagnosis of PCOS was based on evidence of hyperandrogenemia (free androgen index, FAI>5) with a history of oligomenorrhea (cycle length <21 or >35 days; <8 cycles per year). Women with no classical 21-hydroxylase deficiency, hyperprolactinemia, adrenal or ovarian tumor and Cushing's disease were excluded by the appropriate tests. Other exclusion criteria were hypertension, thyroid dysfunction, overt diabetes mellitus and concomitant treatment, such as antihypertensive drugs, selective serotonin reuptake inhibitor or other SNRI drug, oral contraceptive pills or any other antiandrogen treatment (cyproterone acetate, spirolactone, luteinizing hormone (LH) release hormone agonist) and insulin-sensitizing agents (metformin, pioglitazone, rosiglitazone) that may interact with insulin sensitivity and lipid profile.

Written informed consent was obtained from each woman. The study was conducted at the Division of Endocrinology and Human Reproduction outpatient clinic after receiving approval from the National Ethics Committee of the Hellenic Drug Organization. The trial was conducted in accordance with the guidelines of the Helsinki declaration. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. A total of 84 women with PCOS were recruited and 59 of them completed the study (Figure 1).

Study design

This was a prospective, open-label, randomized, comparative trial. The study design included three periods; a screening period to confirm the PCOS diagnosis, a run-in period (4 weeks duration) that all patients received 10 mg per day sibutramine plus a 600 kcal deficient diet, a treatment period (for the subsequent 6 months) that subjects were randomized in a 2:1 ratio to the S group (10 mg per day of sibutramine plus hypocaloric diet) and the D group (hypocaloric diet only). The run-in period was adopted by all patients, to achieve a substantial weight loss and therefore increase compliance to treatments. Diet was based on

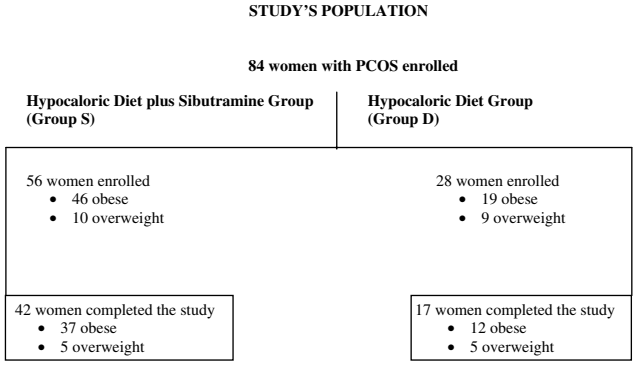

Figure 1 Schematic presentation of the study population.

individual basal metabolic rate as defined by the Harris-Benedict equation, adjusted for moderate physical activity. Before entering the run-in period all subjects were prescribed an energy-restricted diet containing 50% of energy as carbohydrate, 30% of fat (10% saturated) and 20% of protein. Subjects were advised not to modify their eating habits throughout the study period. The randomization was performed using sealed envelopes prepared in advance of the study by a research associate not involved in the study. A randomization table was created using blocks of three numbers with all possible combinations, to achieve the randomization 2:1 ratio to S and D groups. A random number generator was used to keep balance between treatment groups. Abbott Laboratories Hellas provided the study drug.

Clinical measures

Body weight, waist circumference and fasting blood samples for the determination of total testosterone (T), SHBG, dehydroepiandrosterone sulfate (DHEAS), androstenedione (Δ4A), 17a-hydroxyprogesterone, follicle-stimulating hormone (FSH), LH, thyroid-stimulating hormone, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), glucose and insulin were taken at baseline as well as at 3 and 6 months of treatment. At the same time, an oral glucose tolerance test (OGTT) with 75 g glucose was performed.

Blood samples were collected between 0830 and 0900 hours, after an overnight fast, always between days 3 and 7 of women's menstrual cycle (follicular phase). IR was calculated using (1) the homeostasis model of assessment of insulin resistance, HOMA-IR (insulin ($\mu U\,ml^{-1}$) × glucose ($mmol\,l^{-1}$)/22.5),[25] and (2) the area under the curve (AUC) for glucose. This area was calculated from values at 0 (fasting), 30, 60, 90 and 120 min of the OGTT with the trapezoid rule. Monthly, subjects' body weight was recorded, adverse events, heart rate, blood pressure and study drug compliance were determined, and a pregnancy urine test was carried out. Body weight was always measured at morning hours with subjects in light clothing.

Study measurements and assays methods

Plasma glucose concentration was determined with the glucose oxidase method using an autoanalyser (Roche/Hitachi 902; Roche Diagnostics GmBH, Manheim, Germany). LH, FSH, prolactin (PRL), androgen and 17α-OH-progesterone (data not shown) levels were measured with radioimmunoassay, while SHBG levels were determined with immunoradiometric assay (IRMA) method, using commercial kits (FSH, LH and PRL: Radioisotopic Kit, Nichols Institute Diagnostics, San Juan Capistrano, CA, USA; T, Δ4A, DHEA-S, 17α-OH progesterone: Radioisotopic Kit, Diagnostic Systems Laboratories, Webster, TX, USA; SHBG: Immunoradiometric Assay (IRMA) Kit, Diagnostic Systems Laboratories, USA. Serum insulin was measured with an enzyme immunoassay (ELISA Kit, Mercodia AB, Uppsala, Sweden).

The intra-assay coefficients of variation (CV) were 1.5% for FSH, 0.7% for LH, 2.7% for PRL, 1.3% for T, 5.9% for Δ4A, 9.4% for DHEA-S, 5.8% for SHBG and 3.8% for insulin. The average inter-assay CV were 3.2% for FSH, 1.7% for LH, 3.4% for PRL, 2.2% for T, 9.2% for Δ4A, 12.1% for DHEA-S, 7.8% for SHBG and 4.4% for insulin.

Calculations

Body mass index was calculated as weight (kg) divided by height (m) squared. Waist and hip circumferences were measured in duplicate at the upright position, and their ratio (WHR) was calculated. FAI was calculated as: T ($nmol\,l^{-1}$) × 100/SHBG ($nmol\,l^{-1}$).[26]

Statistical analysis

The normality of distribution was checked for all variables with the Kolmogorov–Smirnov test. All variables were normally distributed. Statistical analysis was performed using the absolute values as well as the percentage change from baseline at 3 and 6 months of treatment. Percent changes from baseline and the percent change difference between groups were evaluated with the Student's *t*-test for independent samples. Comparisons of means between groups throughout the measurement time points were performed with repeated measures two-way analysis of variance. An analysis of covariance (ANCOVA) was employed to test the differences in FAI and glucose AUC. Body weight at each time point was used as covariate in the former analysis and body weight and total testosterone were the covariates in the latter analysis. Effect of treatment (time) was set as the within-subjects factor, with group (D or S) as the between-subjects factor. *Post hoc* analysis was performed after Bonferroni adjustment when F was significant for the interaction. Comparison of frequencies for women losing more than 10% of their initial body weight in each group was performed using χ^2-test. Finally, the relations between variables were tested with the Pearson's correlation coefficient. All analyses were performed by the statistical package SPSS, v.13.0 (SPSS Inc., Chicago, IL, USA). Two-tailed statistical significance was set at 5%. Data are presented as mean ± standard error of the mean (s.e.m.).

Results

Body weight and body fat distribution

Mean age was 23.5 ± 1.1 (range 18–36) years in group D and 25.2 ± 0.9 (range 18–39) years in group S. The median (range) BMI was 33.70 (30.12–42.37) $kg\,m^{-2}$ and 34.60 (30.14–52.48) $kg\,m^{-2}$ in groups D and S, respectively. At baseline, 5 women were overweight (29.4%) and 12 obese (70.6%) in group D

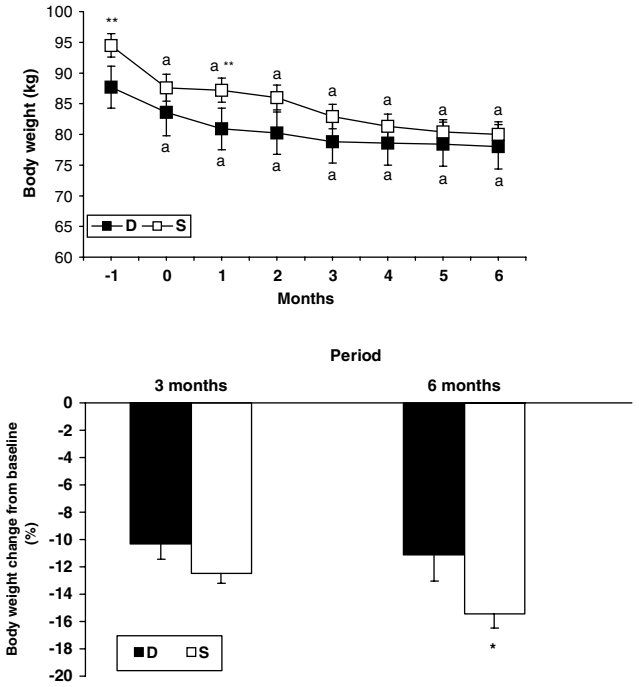

Figure 2 Mean body weight (upper part) and body weight changes (lower part) in overweight and obese women with PCOS placed on a hypocaloric diet (D, $N=17$) and hypocaloric diet plus sibutramine (S, $N=42$) for 6 months. −1, baseline measurement; 0, end of run-in period; $^{a}P<0.001$ from baseline; $^{*}P<0.05$ between groups. $^{**}P<0.01$ between groups.

whereas 5 women were overweight (11.9%) and 37 obese (88.1%) in group S.

Body weight at baseline was higher in group S than D (94.5 ± 1.9 vs 87.7 ± 3.4 kg, $P<0.01$; Figure 2), but this difference disappeared at the end of the run-in period (S, 87.6 ± 2.2 kg; D, 83.6 ± 3.8 kg; $P=0.34$). Percent change in body weight at the end of run-in period did not differ between groups (S, −5.3 ± 0.3%; D, −5.0 ± 0.4%). After 3 and 6 months of treatment, body weight and BMI were lower compared with baseline in both groups ($P<0.05$). However, women who received sibutramine presented lower ($P<0.05$) body weight and BMI at 6 months compared with 3 months measurement (Figure 2). After 6 months, percent change in body weight was greater in group S than D (−15.4 ± 1.1 vs –11.1 ± 1.9%, respectively, $P<0.05$). A greater percent of women lost more than 10% of their initial body weight in this 6-month period in group S than in the group D (81 vs 52.9%, respectively, $\chi^2=4.804$, d.f. = 1, $P<0.05$).

At the end of study, 15 obese women at baseline became overweight (40.5% of obese at baseline) and 7 became normal (18.9%) in group S. In group D, five obese women at baseline became overweight (41.7%) and one obese became normal (8.3%) at the end of 6 months. Finally, central adiposity was reduced in both groups as indicated by the lower waist circumference at 3 and 6 months compared to baseline ($P<0.05$; Table 1).

Androgens

Percent change from baseline in T and SHBG at 6 months was significant in group S only ($P<0.01$; Table 1). FAI was lower with sibutramine after 3 and 6 months of treatment compared with baseline when an ANCOVA was employed with body weight at each measurement time as covariates (Figure 3). No such decline was seen in the hypocaloric diet group. Finally, the percent decline in FAI after 6 months compared with baseline, was greater in group S than in D (−29.7 ± 4.8 vs 2.7 ± 11.6%, respectively, $P<0.01$).

Insulin, glucose and insulin resistance

At baseline, 14 of 42 women had an abnormal OGTT (33.3%) in group S and 4 of 17 women (23.5%) in group D. At the end of the study, no subject had an abnormal OGTT in group S whereas only one woman had an abnormal OGTT in group D. Fasting insulin and HOMA-IR did not differ between groups (Table 1). Glucose AUC was lower after 6 months of treatment compared with baseline in group S (964.0 ± 25.5 vs 819.7 ± 25.3 mmol per min per l, $P<0.05$), when ANCOVA was employed with body weight and total testosterone as covariates (Figure 3). Percent change in AUC at 6 months, compared to baseline, was also greater in group S than D ($P<0.05$).

Blood lipids, prolactin levels, hepatic enzymes and cardiovascular risk factors

Blood lipids as well as serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and γ-glutamyl transferase (γGT) concentrations did not differ between groups at baseline (Table 1). Percent reduction in TG was greater in group S than in D ($P<0.05$). In addition, percent change from baseline at 6 months was significant in group S for TC ($P<0.05$), HDL-C ($P<0.05$), SGOT ($P<0.05$), SGPT and γGT ($P<0.01$), systolic ($P<0.01$) and diastolic ($P<0.01$) blood pressure (Table 1). Prolactin levels were unchanged in both groups (Table 1).

Correlations

In the sibutramine group ($N=42$), percent decline in body weight after 6 months was correlated with percent changes in FAI ($r=0.337$, $P<0.05$), SHBG ($r=-0.467$, $P<0.01$), fasting insulin ($r=0.575$, $P<0.01$), SGOT ($r=0.397$, $P<0.01$) and γGT ($r=0.35$, $P<0.05$). When data were analyzed for the hypocaloric diet group ($N=17$), percent decline in body weight after 6 months was associated with the percent changes in the hepatic enzymes only ($r=0.484$ and 0.559 for SGPT and γGT, $P<0.05$).

Subject's compliance rate and adverse events

Fourteen women (nine obese and five overweight) were lost to follow-up during the first 2 months of treatment in group

Table 1 Anthropometric data, metabolic and cardiovascular variables at baseline, after 3 and 6 months of treatment with hypocaloric diet ($N=17$) and hypocaloric diet plus sibutramine ($N=42$) in overweight and obese women with PCOS

Variable	*Diet plus sibutramine (group S)*			*Hypocaloric diet (group D)*		
	Baseline	*3 months*	*6 months*	*Baseline*	*3 months*	*6 months*
Age	25.2 ± 0.9			23.5 ± 1.1		
Weight (kg)	94.5 ± 1.9**	82.9 ± 2.0[a]	80.0 ± 2.1[a,b]	87.7 ± 3.4	78.8 ± 3.5[a]	78.0 ± 3.6[a]
Waist circumference (cm)	99.5 ± 1.3**	89.5 ± 1.4[a]	86.9 ± 1.4[a,b,c]	94.1 ± 2.4	86.4 ± 2.7[a]	85.4 ± 2.8[a,c]
WHR	0.84 ± 0.00	0.82 ± 0.00	0.82 ± 0.00[c]	0.82 ± 0.00	0.79 ± 0.00	0.78 ± 0.00[c]
BMI (kg m^{-2})	34.4 ± 0.6	30.1 ± 0.8[a]	29.1 ± 0.8[a,b,c]	33.0 ± 1.0	29.6 ± 1.1[a]	29.3 ± 1.1[a,c]
Fasting insulin (μmol l^{-1})	143.6 ± 11.5	86.1 ± 6.5	84 ± 7.9[c]	127 ± 14.3	73.2 ± 9.3	81.1 ± 14.3[c]
Fasting glucose (mmol l^{-1})	5.87 ± 0.10	5.60 ± 0.09	5.65 ± 0.11	5.76 ± 0.16	5.51 ± 0.18	5.51 ± 0.12
HOMA-IR	5.4 ± 0.5	3.0 ± 0.2	2.9 ± 0.3[c]	4.5 ± 0.5	2.5 ± 0.3	2.8 ± 0.6[c]
Total testosterone (nmol l^{-1})	2.78 ± 0.15	2.24 ± 0.11	2.23 ± 0.10[c]	2.67 ± 0.18	2.31 ± 0.18	2.58 ± 0.15
SHBG (nmol l^{-1})	26.1 ± 1.7	34.7 ± 3.4	34.7 ± 3.0[c]	28.3 ± 2.7	30.2 ± 2.1	30.2 ± 2.8
Δ4A (nmol l^{-1})	9.77 ± 0.69	9.07 ± 0.69	9.07 ± 0.35	10.12 ± 1.05	10.47 ± 1.39	11.16 ± 1.05
DHEA-S (μmol l^{-1})	8.55 ± 0.55	8.73 ± 0.6	8.22 ± 0.57	9.2 ± 0.93	8.94 ± 0.77	9.04 ± 0.65
FSH (U l^{-1})	5.28 ± 0.17	4.47 ± 0.29	4.49 ± 0.29[d]	5.22 ± 0.35	4.72 ± 0.45	4.74 ± 0.38
LH (U l^{-1})	7.25 ± 0.68	9.01 ± 1.26	7.99 ± 0.82[d]	7.29 ± 0.8	8.17 ± 1.67	9.90 ± 1.40[d]
PRL (mU l^{-1})	250 ± 14	254 ± 18	254 ± 18	258 ± 28	244 ± 20	294 ± 32
TG (mmol l^{-1})	1.30 ± 0.08	0.98 ± 0.06	0.94 ± 0.06[c]	1.04 ± 0.11	1.01 ± 0.10	1.02 ± 0.09
Total cholesterol (mmol l^{-1})	4.95 ± 0.13	4.59 ± 0.13	4.62 ± 0.13[d]	4.7 ± 0.17	4.6 ± 0.24	4.6 ± 0.23
HDL-C (mmol l^{-1})	1.13 ± 0.02	1.09 ± 0.02	1.18 ± 0.03[d]	1.18 ± 0.05	1.15 ± 0.04	1.15 ± 0.04
LDL-C (mmol l^{-1})	3.23 ± 0.11	3.01 ± 0.10	3.00 ± 0.11	3.03 ± 0.15	3.06 ± 0.18	2.99 ± 0.20
SBP (mm Hg)	112.7 ± 2.1	107.3 ± 1.7	105.8 ± 1.8[c]	106.8 ± 3.8	101.5 ± 2.6	100.9 ± 1.8[c]
DBP (mm Hg)	75.8 ± 1.5	75.1 ± 1.5	71.0 ± 1.4[d]	72.4 ± 2.5	69.4 ± 1.9	67.4 ± 2.6[d]
HR (beats per min)	78.8 ± 1.4	84.9 ± 2.0	83.9 ± 2.1	76.1 ± 2.6	75.8 ± 3.3	80.8 ± 3.2
SGOT (U l^{-1})	19.1 ± 0.8	17.7 ± 0.7	16.8 ± 0.6[d]	19.8 ± 1.9	19.0 ± 1.7	17.4 ± 1.4
SGPT (U l^{-1})	24.6 ± 2.0	17.9 ± 1.6	17.1 ± 1.5[c]	22.7 ± 3.2	17.1 ± 3.1	17.1 ± 3.2[d]
γGT (U l^{-1})	22.5 ± 1.5	18.4 ± 1.5	18.0 ± 1.1[c]	22.1 ± 2.5	17.2 ± 2.4	21.2 ± 3.4

Abbreviations: Δ4A, androstenedione; BMI, body mass index; DBP, diastolic blood pressure; DHEA-S, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; γGT, γ-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, heartrate; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; PRL, prolactin; SBP, systolic blood pressure; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; SHBG, sex hormone-binding globulin; TG, triglyceride; WHR, waist-to-hip ratio. Mean ± s.e.m. [a]$P<0.01$ from baseline. [b]$P<0.05$ from 3 months measurement. *$P<0.05$ and **$P<0.01$ compared with the hypocaloric diet group. [c,d]Percent changes are significant from baseline ($P<0.01$ and $P<0.05$, respectively).

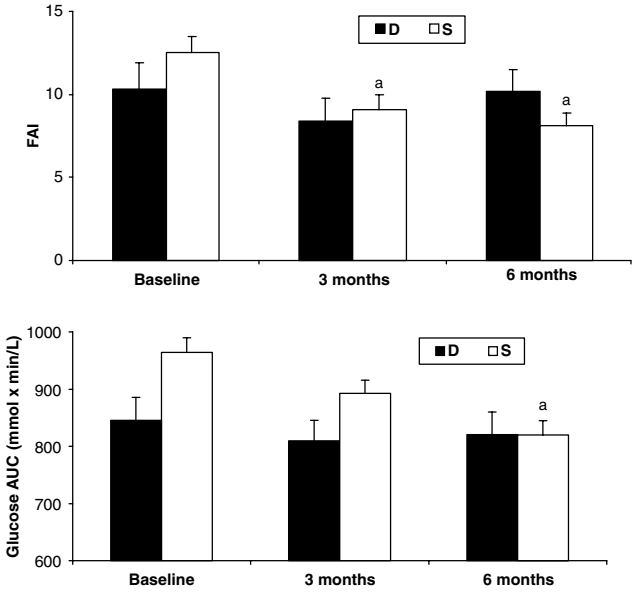

Figure 3 Free androgen index values (FAI, upper part) and glucose area under the curve (AUC, lower part) after 24-week treatment with hypocaloric diet (D, $N=17$) and hypocaloric diet plus sibutramine (S, $N=42$) in overweight and obese women with PCOS. [a]$P<0.001$ from baseline.

S (25% drop out rate) and eleven women (seven obese and five overweight) in group D (39.2%). No serious adverse effects were reported during the study period.

Discussion

The main finding of this study was that a hypocaloric diet and a diet supplemented with sibutramine both reduce body weight within 3 months in overweight and obese women with PCOS. However, body weight decline was more pronounced in the group of women who received sibutramine, while women on diet only showed a plateau in the second trimester of treatment.

More patients achieved greater than 10% weight loss, which is considered of clinical significance, when diet was supplemented with sibutramine. This could be attributed to the greater patient compliance with the drug. In the sibutramine group, hyperandrogenemia and IR were also ameliorated. This is the first study to compare the effect of a low-calorie diet and diet plus sibutramine on body composition, hormonal and metabolic features in PCOS women. A previous investigation in obese patients with PCOS showed a

15.5% reduction in body weight after 6 months of treatment with sibutramine.[24] However, a direct comparison of the present with the above-mentioned study cannot be made due to the different protocols employed. The greater weight loss in the sibutramine group in the present study could be due to the sibutramine's mode of action. Sibutramine increases satiety, results in greater weight loss compared to diet alone and thus elevates subjects' motivation. This could explain the higher compliance with sibutramine, compared to diet only, in the present study. In addition, sibutramine exerts a thermogenic effect and this could also partially explain the greater decline in body weight with sibutramine.[27,28] Another mechanism for the greater reduction in body weight in the sibutramine compared to the diet group could be the maintenance of plasma leptin levels with sibutramine, as previously shown.[29,30]

Hyperandrogenemia was reduced in both groups in the present study and this reduction was more pronounced in the sibutramine group, as evidenced by the greater decline in FAI from baseline at 6 months of treatment (Figure 3). In addition, total testosterone levels decreased and SHBG increased in group S, indicating that weight loss with diet plus sibutramine may improve hyperandrogenemia and hirsutism. These findings are in accordance with previous clinical studies.[17–19,23,31,32] The reduction in FAI could be, at least in part, due to the greater weight loss in group S than D. A previous report in PCOS women showed a reduction in hyperandrogenemia with sibutramine treatment in such patients.[24]

It is of note that all subjects with glucose intolerance at baseline presented a normal OGTT at 6 months of treatment, except for one. This finding is in agreement with the view that weight loss *per se* is the most important factor for improvement in glucose metabolism in previously obese patients with abnormal carbohydrate metabolism. An interesting finding of the present study was that insulin sensitivity, as examined with the OGTT AUC, was improved at 6 months of treatment in S group (Figure 3), and this effect was not totally explained by the reduction in body weight and total testosterone levels. The improvement in IR with sibutramine is in accordance with other studies.[24,33,34] It is difficult to speculate on the effect of sibutramine on IR. Central obesity and in particular the amount of visceral fat is associated with IR in obese patients. Waist circumference change did not differ between conditions in the present study. However, this finding does not exclude the possibility that visceral fat reduction might have been greater in the sibutramine group, as previously shown with such treatment in obese patients.[29]

The amelioration of hyperandrogenemia and the reduction in TG concentration in group S could be an explanation for the improvement in IR. In the present study, a 12–14% reduction in body weight with sibutramine or diet only did not affect insulin sensitivity in these patients, whereas a beneficial effect was observed at about 15.5% reduction of the initial body weight in the sibutramine group. This percent reduction coincided with 6 months treatment with sibutramine. Based on this observation we could speculate that there is a critical weight loss, which seems to be around 15%, to observe a significant improvement in IR in women with PCOS. Given the greater reduction in TG concentration with sibutramine, compared to diet-only in the present study, we could also speculate that this reduction contributed to the greater insulin sensitivity observed in the former group. This finding suggests an essential role of free fatty acids in the pathogenesis of IR in obesity.

Prolactin was unchanged and this is also of interest since sibutramine is a weak reuptake inhibitor of dopamine and prolactin levels may be moderately increased in PCOS women.[35] However, prolactin levels at baseline were within the normal range in these women and this should be kept in mind when interpreting these data.

It has been reported that sibutramine may cause a mild elevation in heart rate and blood pressure. However, studies with sibutramine have shown an improvement in blood pressure in obese hypertensive and normotensive patients suggesting that body weight reduction *per se* may alleviate this potentially harmful effect of sibutramine.[36–38] In the present study, the reduction in blood pressure was significant from baseline whereas heart rate did not change with sibutramine. It should be noted, however, that our study population was young normotensive women without pre-existing cardiovascular disease.

Fasting leptin levels and insulin concentration during the OGTT were not determined and these are limitations of this study. In addition, insulin sensitivity was evaluated with OGTT, which is an indirect method for insulin-sensitivity assessment. The mechanism for insulin sensitivity improvement with sibutramine treatment in PCOS women should be explored in future studies. Although the used method for determining testosterone levels is not precise, all the currently commercially available testosterone RIAs suffer from reliability regarding sensitivity, specificity and intra-assay variability.[39,40] Nevertheless, all participating women to this study had confirmed diagnosis of PCOS based on oligomenorrhea, clinical consequence of chronic anovulation, the clinical hyperandrogenism and the appearance of PCO morphology in the ultrasound examination.

In conclusion, a hypocaloric diet and diet plus sibutramine both result in significant weight loss in overweight and obese women with PCOS. However, body weight reduction was more pronounced in women receiving sibutramine. Sibutramine treatment also resulted in amelioration of hyperandrogenemia and IR in these women. The improvement in insulin sensitivity in women who received sibutramine could not be totally explained by weight loss. Total testosterone, FAI and TG levels reduction could be a possible additional mechanism, but further studies are needed to explore these findings. It seems that a hypocaloric diet supplemented with sibutramine increases the patients' compliance to diet.

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