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Spironolactone in the treatment of polycystic ovary syndrome: Effects on clinical features, insulin sensitivity and lipid profile

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ABSTRACT. This prospective clinical trial was designed to assess the effects of a long-term therapy with spironolactone, with and without dietary-induced weight-loss, on clinical features, lipid profile and insulin levels in women with polycystic ovary syndrome (PCOS). Twenty-five patients (range of age 16-32 yr; 13 lean and 12 overweight) fulfilling formal diagnostic criteria for PCOS (oligomenorrhea and/or amenorrhea, biochemical and/or clinical evidence of hyperadrogenism) were studied at baseline and then received oral spironolactone (100 mg/*die*) for 12 months; association with lifestyle modifications was recommended to all overweight patients. Clinical, endocrine and metabolic parameters [oral glucose tolerance test (OGTT), lipid profile] were measured at baseline and at the end of the antiandrogen treatment. The therapy was associated with a significant average decline of triglycerides in overweight subjects and with increased HDL-cholesterol levels in lean patients. The insulin levels at 60 min during OGTT, homeostasis model assessment-insulin resistance and area under curve of insulin were significantly lowered in overweight women after 12 months of spironolactone and weight loss and no negative changes in insulin secretion and sensitivity were observed in PCOS women after pharmacological treatment alone. The efficacy of spironolactone on the androgenic clinical aspects of PCOS has been confirmed in this study. Furthermore, our data show that long-term treatment with spironolactone exerts no negative effects on lipoprotein profile and glucose metabolism; more relevant beneficial effects on glucose and lipid metabolism were observed when the antiandrogen was associated with weight loss in overweight PCOS women.
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INTRODUCTION

Polycystic ovary syndrome (PCOS) is present in approximately 4-7% of reproductive-aged women, and insulin resistance and hyperinsulinism affect a large part of them (1). Insulin resistance, combined with the worsening effect of obesity (which seems to affect 50-55% of the PCOS population), places those women at increased risk for impaired glucose tolerance (IGT) and, most likely, diabetes mellitus (DM) (2, 3). Insulin may affect the ovary in multiple ways, and there are suggestions that the net effect may be a disturbed ovulation and/or an increased androgen production in many cases (4, 5). On the other hand, androgens may induce insulin resistance, through changes in muscle fiber structure. As androgen excess and hyperinsulinemia contribute to a different degree on the PCOS, therapeutic efforts have been focused on agents which could treat or modify both cluster of clinical manifestations (6).

Most reports suggest that the lipid profile of women with PCOS is characterized by elevated serum levels of total cholesterol (TC), low density lipoproteins (LDL), very low density lipoproteins (VLDL), and triglycerides (TGC) with concomitant reduction of HDL cholesterol (7). These abnormalities in lipid levels have serious atherogenic consequences. High LDL and low HDL, in fact, predict the development of coronary heart disease, as observed in the Framingham's study (8). It is well known that in PCOS obesity is associated with menstrual disorders (9), while weight reduction restores obesity-related menstrual disorders and infertility (10). Lifestyle modifications, such as food restriction and physical activity, are

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then likely to be the first and most recommended approach in overweight women with PCOS.
The present study was designed to assess the efficacy of a long-term oral treatment with spironolactone (used as a single agent, 100 mg/die) on clinical features, metabolic profile in lean and obese women with PCOS. A low calorie diet associated with pharmacological treatment was recommended to all our overweight patients, but only in a subgroup of them we could observe a significant weight loss. After 12 months, overweight women could then be divided into 2 groups, the comparison of these being of great interest in order to define the contribution of weight loss to the decrease in insulin secretion.

MATERIALS AND METHODS

Patients

Twenty-five women, aged between 16 and 32 yr, were recruited for the study. All these subjects were referred to our division for menstrual abnormalities, with hirsutism and/or acne and alopecia. All subjects were in good health and none of them had received any drugs known to interfere with hormonal levels in the last 3 months. Diagnosis of PCOS was based on the presence of chronic anovulation (oligomenorrhea and/or amenorrhea), one or more signs of clinical hyperandrogenism, such as acne, alopecia, seborrhoea and hirsutism with a modified Ferriman-Gallwey (F.G.) score >8, and/or endocrinological abnormalities (increased testosterone, DHEA-S and/or androstenedione concentrations in the early follicular phase).
Thyroid function and PRL secretion were normal. Cushing's syndrome and congenital adrenal hyperplasia were excluded.
The research protocol was approved by the local ethic board. Informed written consent was obtained from all participants (and at least one parent when the subject was <18 yr of age).

Protocol

Clinical features, such as body mass index (BMI), F.G. score, acne (classified according to Lucky's score) (11), alopecia [classified according to Ludwig's score (12)], blood pressure (BP), endocrine (LH, FSH, testosterone, DHEA-S, androstenedione, PRL) and metabolic (TGC, TC, HDL) parameters, were evaluated in lean and overweight patients with PCOS. An oral glucose tolerance test (OGTT) was performed in all patients, without regard to their personal or family history of glucose intolerance.
The BP was measured in the right upper arm with a standard sphygmomanometer in the sitting position.
The baseline evaluations were performed as follows: blood samples were collected at 08:00 h after an overnight fast to determine serum levels of steroids (testosterone, androstenedione, DHEA-S) and lipids (TC and HDL-cholesterol, TGC).
The OGTT was performed after an overnight fast of at least 10 h. A fasting blood sample was obtained at time 0 (between 08:00 and 10:00 h) for measurement of glucose and insulin levels; another blood sample was obtained 60 and 120 min after oral administration of 75 g glucose. Glucose tolerance was evaluated using the criteria of the World Health Organization. Homeostasis model assessment-insulin resistance ($HOMA_{IR}$) was calculated according to the formula [plasma glucose (mmol/l) x insulin (μU/ml): 22.5] (13).
The insulin response to the OGTT was also expressed as area under the curve ($AUC_{insulin}$) estimated by the trapezoidal rule.
After 12 months of oral spironolactone (100 mg/die) and lifestyle modifications, such as food restriction (1400 kCal/die), associated with pharmacological therapy in overweight PCOS patients, the following parameters were evaluated: menstrual record, BMI, BP, F.G. score, TGC, TC, HDL, OGTT, $AUC_{insulin}$, $HOMA_{IR}$.

Assay methods

Plasma insulin was measured by a specific immunometric assay (IMMULITE 2000 Analyser®, Diagnostic Products Corporation). Serum gonadotropins and androgens were measured by immunoradiometric assay. TC, HDL and TGC were determined by the enzyme calorimetric method (HITACHI 747®, Roche).

Statistical method

Data are presented as mean±SD; comparison of means was performed using student t-test for paired data or analysis of variance (ANOVA), as appropriate.

RESULTS

Our patients were divided into two subgroups (Table 1): 13 lean and 12 overweight patients were studied at baseline, and treated with oral spironolactone (100 mg/die) for one yr and then restudied. Lifestyle modifications, such as food restriction (1400 kcal/die), were associated with pharmacological therapy in overweight patients, but in 5 of them the weight was almost unchanged after 12 months (group A). Data coming from overweight women, whose weight was significantly reduced during the 12-month therapy (group B), are reported in Table 2.
The treatment with spironolactone showed its clinical efficacy both in lean and in overweight women as F.G. scores were significantly lowered from 12.2±2.5 to 6.8±3.7 (p=0.0003) and from 10.1±2.93 to 5.25±2.6 (p=0.0002), respectively. Acne was observed in 4 lean women (31%) and in 4 overweight women (33%) at baseline; we noticed a regression of the disorder in 1 of the lean and in 3 of the overweight acne-affected women after the treatment. Alopecia, which affected 7 women (3 lean and 4 overweight) at baseline, regressed only in 2 subjects after spironolactone. Cycle menses were irregular in all our patients at baseline; 21 reported oligomenorrhea and 4 amenorrhea. After treatment, cycle menses became regular in the lean and in 4 overweight women (1 of group A, 3 of group B). Three lean and 4 overweight women referred polymenorrhea during treatment.
There was a trend among overweight patients to have higher levels of TGC and TC before and after treatment; the therapy was associated with a significant average decline of TGC in overweight patients

Table 1 - *Clinical features and metabolic profile at baseline and after treatment in lean and overweight polycystic ovary syndrome (PCOS) women.*

	BMI<25 (no.=13)		BMI>25 (no.=12)	
	Baseline	After treatment	Baseline	After Treatment
Age (yr)	23.8±4.9	–	22.3±5.6	–
Score F.G.	12.2±2.5	6.8±3.69	10.1±2.9	5.2±2.6
BP (systolic) (mmHg)	126.5±19.1	115.8±7.0	121.7±10.5	118.3±10.3
BP (diastolic) (mmHg)	80±3.9	75.4±5.2	79.6±3.3	77.9±5.4
BMI (kg/m^2)	22.4±2.3	22.3±2.4	29.4±4	27.4±4.7*
TGC (mmol/l)	0.88±0.2	0.97±0.7	1.54±0.1	1.20±0.6*
TC (mmol/l)	4.35±1.5	4.6±1.3	4.48±0.4	4.78±0.7
HDL-cholesterol (mmol/l)	1.11±0.3	1.47±0.1*	1.18±0.1	1.19±0.15
Fasting glucose (mmol/l)	4.9±0.6	4.66±0.4	4.9±0.4	4.8±0.6
75-g OGTT 60 min (mmol/l)	7.55±1.4	5.9±1.3	6.8±2.3	5.9±1.4
75-g OGTT 120 min (mmol/l)	5.5±1.3	4.6±1.2	5.8±1.7	5.1±1.45
Fasting insulin (mmol/l)	9.1±3.6	10.2±2.8	17.25±5.9	14.9±6.4
75-g OGTT 60 min (mmol/l)	39.5±15.43	39.7±14.6	67.3±13.9	51.8±24.7*
75-g OGTT 120 min (mmol/l)	40.7±32.5	31.6±14.25	38.2±20.4	27.8±20.5
$HOMA_{IR}$	2.02±0.9	2.1±0.7	3.6±1.1	2.9±1.7
$AUC_{insulin}$	3860±1300	3635±1250	6002±2962	4710±2074*

Values are given as mean±SD. Asterisks indicate significant differences between baseline and after treatment data. (*p<0.05). BP: blood pressure; BMI: body mass index; TGC: triglicerides; OGTT: oral glucose tolerance test; $HOMA_{IR}$: homeostasis model assessment/insulin resistance; F.G.: Ferriman-Gallway.

(–22%, p<0.05) and with an increased level of HDL in lean patients (–24%, p<0.05). We also observed increased levels of TC both in lean and in obese women and increased levels of TGC in lean women (not statistically significant) after 12 months. The insulin levels at 60 min after oral glucose challenge

Table 2 - *OGTT, $HOMA_{IR}$, $AUC_{insulin}$ and lipid profile in group A (spironolactone) and group B (spironolactone and dietary induced weight-loss) at baseline and after treatment.*

	Group A (no.=5)		Group B (no.=7)	
	Baseline	After therapy	Baseline	After therapy
Age (yr)	19.8±5	–	24±5.7	–
BMI (kg/m^2)	28.6±4.7	29±5.4	30.3±3.5	26.3±3.4*
Score F.G.	10.6±2.7	5.6±2.7	9.7±3.3	5±2.8
Fasting glucose (mmol/l)	5.1±0.1	4.9±0.6	4.8±0.5	4.7±0.5
75-g OGTT 60 min (mmol/l)	6.7±1.5	6.6±1.5	6.9±2.9	5.4±1.3
75-g OGTT 120 min (mmol/l)	5.4±1.3	5.2±1.6	6±2	5±1.4
Fasting insulin (mmol/l)	18.2±6.8	16.4±3.6	17.4±3.4	13.9±8
75-g OGTT 60 min (mmol/l)	73.4±15.5	66.6±17.8	63±14	41.3±24.3*
75-g OGTT 120 min (mmol/l)	46.8±13.3	45±21.6	32±23.3	15.57±6.4
$HOMA_{IR}$	4.1±1.5	4.2±1.8	3.2±0.4	1.9±0.6*
$AUC_{insulin}$	5880±1592	5004±2189	6090±3791	4500±2120*
TG (mmol/l)	1.5±0.1	1.2±0.3*	1.6±0.1	1.2±0.2*
TC (mmol/l)	4.52±0.5	4.68±0.8	4.45±0.4	4.85±0.4
HDL-cholesterol (mmol/l)	1.16±0.1	1.18±0.2	1.2±0.1	1.2±1.5

Values are given as mean±SD. Asterisks indicate significant differences between baseline and after treatment data. (*p<0.05). $AUC_{insulin}$: area under the curve of insulin; BMI: body mass index; F.G.: Ferriman-Gallway; $HOMA_{IR}$: homeostasis model assessment-insulin resistance; OGTT: oral glucose tolerance test. TGC: Tryglicerides; TC: Total cholesterol.

were significantly lowered in obese women after 12 months of food restriction and spironolactone, and no significant changes were observed in PCOS women (lean and overweight) after pharmacological treatment alone. If group A and B are compared, the decrease of BMI, insulin levels 60 min after 75 g glucose load, $HOMA_{IR}$ and $AUC_{insulin}$ remains significant only in group B.

DISCUSSION

Antiandrogenic properties of spironolactone have been demonstrated in several experimental models, and its efficacy in treatment of acne, alopecia, seborrhoea and hirsutism is well established, so that it is nowadays frequently used for this purpose (14). F.G. score was indeed decreased in all our patients, both in lean and in the two groups of overweight women.

The tolerability of spironolactone was good in our patients. It is known that spironolactone may cause polyuria and polydipsia, particularly in the first days of treatment, and occasionally it can produce headaches, increased appetite and body weight, breast enlargement and tenderness, and dizziness (15). Our patients did not notice any of these side effects over the treatment period.

The only unwanted effect of the therapy was polymenorrhea, which was however not relevant enough to withdraw from the treatment.

Our study focused on the evaluation of the metabolic parameters. It is undeniable that the possibility of ameliorating insulin secretion and lipid profile by the treatment of hyperandrogenism would be of great interest and of important therapeutic value. Most studies have shown that insulin resistance is poorly improved in PCOS patients receiving blockers of androgen receptors or other drugs which suppress ovarian androgen secretion. Only a minority of researchers could however demonstrate that antiandrogen treatment partially reverses the defect in insulin sensitivity (16).

Our data, especially those coming from the comparison between the 2 subgroups of overweight women, showed a significant decrease of insulin in patients who associated lifestyle modifications to pharmacological therapy. Both $HOMA_{IR}$ and $AUC_{insulin}$ were significantly decreased after 12 months, while they were unchanged in patients treated with spironolactone alone without a decrease of BMI. It is worth noting that in patients treated with spironolactone alone (lean and overweight group A patients) glucose metabolism, as well as lipid profile, was not impaired by long term therapy.

In women with PCOS, the comparison of different treatment regimens (including combined oral contraceptives and spironolactone) showed that HDL cholesterol levels were increased (17). Wild et al. (18) reported that long-term treatment with oral contraceptives was associated with increased triglycerides levels, which was not observed in women treated with spironolactone.

Most of the subjects of the present trial were not affected with dyslipidemia. We could observe increased levels of HDL cholesterol after therapy, which was significant only in lean subjects. This observation however should be confirmed by studying a more consistent number of subjects. Furthermore, there was a significant decrease in serum TGC in overweight women after pharmacological treatment; this effect may be correlated with food restriction and decrease of BMI rather than with spironolactone treatment. Obesity, which is frequently associated with PCOS, seems to amplify the degree of insulin resistance (19). A number of investigators have confirmed the findings of Dunaif et al., whose studies have established that the magnitude of insulin resistance in PCOS is greater than that which can be accounted for by obesity alone (20). Other studies however were able to show that obese women, especially those with the abdominal obesity phenotype, are more insulin resistant than their normal-weight counterparts (9, 10). In these trials, insulin sensitivity was evaluated by different methods, such as euglycemic hyperinsulinemic clamp technique. Dietary-induced weight loss and the use of insulin-sensitizers, such as metformin, could be viewed in PCOS as a potential strategy for controlling the metabolic alteration and preventing increased susceptibility to developing diabetes in overweight PCOS women. Our data confirm that in obese women with PCOS even partial weight loss may reduce glucose-stimulated insulin levels (9), which was not observed after pharmacological therapy alone.

When it can be achieved, weight loss is probably the ideal treatment for obese women with PCOS.

In conclusion, spironolactone showed its clinical efficacy in the treatment of hyperandrogenism associated with PCOS, and side effects were not remarkable during therapy. Furthermore, our data show that long-term treatment with spironolactone exerts no negative effects on lipoprotein profile and glucose metabolism; while beneficial effects on glucose and lipid metabolism were observed when the antiandrogen was associated with weight loss in overweight PCOS women, whose high degree of insulin resistance and impaired lipid profile are strictly connected with increased risk of cardiovascular and metabolic diseases. In any case, spironolactone seems to exert

a direct effect on the increase of HDL cholesterol independently from weight loss and diet.

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