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 hyperandrogenism) 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.

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
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, DHEAS 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 ethical 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, DHEAS, 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, DHEAS) 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_2) 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_2.

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.