Nutrition, Metabolism & Cardiovascular Diseases (2014) 24, 132–139

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

# In PCOS patients the addition of low-dose spironolactone induces a more marked reduction of clinical and biochemical hyperandrogenism than metformin alone☆

A. Mazza [a], B. Fruci [a], P. Guzzi [b], B. D'Orrico [a], R. Malaguarnera [a], P. Veltri [b], A. Fava [a], A. Belfiore [a,*]

[a] *Department of Health Sciences, Endocrinology, University Magna Graecia of Catanzaro, Campus Universitario, località Germaneto, 88100 Catanzaro, Italy*
[b] *Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro, Campus Universitario, località Germaneto, 88100 Catanzaro, Italy*

Received 29 June 2012; received in revised form 14 April 2013; accepted 17 April 2013
Available online 8 July 2013

**KEYWORDS**
PCOS;
Metformin;
Spironolactone;
Obesity;
Hirsutism;
Insulin resistance

**Abstract** *Background & aims:* Polycystic ovary syndrome (PCOS) is characterized by ovarian dysfunction and hyperandrogenism and by insulin resistance and related metabolic alterations. Both metformin and anti-androgens, such as spironolactone, are used to ameliorate the different aspects of this disorder. We investigated whether therapy with metformin plus low-dose spironolactone is more effective than metformin alone in PCOS patients.

*Methods and results:* Fifty-six PCOS patients were randomized in two groups: group A (28 patients) was treated with metformin (1700 mg/die) and group B (28 patients) was treated with metformin (1700 mg/die) plus low-dose spironolactone (25 mg/die). Anthropometric, hormonal and metabolic parameters were evaluated at baseline and after six months of treatment. After therapy regular menses were restored in approximately 82% of group A patients ($P < 0.001$) and in 68% of group B patients ($P < 0.001$). Circulating testosterone, Δ-4-androstenedione and Hirsutism Score (HS) significantly decreased in both groups. However, dehydro-epiandrosterone sulphate significantly decreased only in group B, and HS underwent a stronger reduction in group B ($P < 0.001$). At baseline, 39/56 (69.6%) patients met the diagnostic criteria for metabolic syndrome, but only one patient met these criteria after treatment.

☆ The trial is registered with Clinicaltrial.gov, number NCT01526616, 27/01/2012.

* Corresponding author. Tel.: +39 0961 3697154.
*E-mail address:* belfiore@unicz.it (A. Belfiore).


http://dx.doi.org/10.1016/j.numecd.2013.04.016

*Conclusions:* This study confirms the beneficial effects of metformin in PCOS patients. It also indicates that the addition of low-dose spironolactone induces a more marked reduction of clinical and biochemical hyperandrogenism as compared to metformin alone.
*Clinicaltrial.gov number:* NCT01526616.


## Introduction

Polycystic ovary syndrome (PCOS) is characterized by a broad spectrum of alterations including hyperandrogenism, ovarian dysfunction and polycystic ovarian morphology [1]. Insulin resistance and compensatory hyperinsulinemia are frequently associated with PCOS, not only in the obese but also in normal weight patients, and are believed to have a pathogenetic role in PCOS. However, visceral obesity is commonly present in PCOS patients and may exacerbate insulin resistance. Therefore, women affected by PCOS develop impaired glucose tolerance (IGT) and T2DM with an increased rate and at younger age as compared to control population matched for weight and ethnic group. Finally, hyperinsulinemia contributes to stimulate hyperandrogenism by multiple mechanisms, including direct effects on ovary thecal cells and adrenal cells, and inhibition of the hepatic synthesis of sex hormone binding protein (SHBG), which increases free testosterone levels.

The therapeutical approach of overweight/obese PCOS patients is currently based on lifestyle intervention. Several studies have shown that these patients benefit from caloric restriction and weight loss, especially when associated to a constant and moderate aerobic physical activity. These lifestyle changes reduce insulin resistance and hyperandrogenism and may restore ovulation [2].

In view of the key role of insulin resistance in PCOS, insulin-sensitizing agents have been evaluated as a rational therapeutic approach in PCOS. In particular, the antidiabetic drug metformin may decrease insulin resistance and serum androgen levels and ameliorate the ovarian function [2]. However, available studies have mostly included patients with various body mass index (BMI) and considered as major end point the ovulation or pregnancy rate and not the associated metabolic alterations.

Anti-androgens are also commonly used in order to block the adverse effects of hyperandrogenism. In particular, spironolactone, an aldosterone antagonist, has a good safety profile, especially when used in small doses. However, studies concerning the use of spironolactone in overweight/obese PCOS patients are very limited. Moreover, no study has assessed the efficacy of a combination therapy with metformin plus spironolactone in overweight/obese PCOS patients.

In the present prospective, randomized study, we evaluated the efficacy of a combined therapy with metformin and low-dose spironolactone as compared to metformin alone on the clinical and endocrine-metabolic alterations of PCOS patients.

## Methods

Our prospective study was carried out in 56 overweight/obese patients with PCOS. Patients were recruited at the Endocrine Unit of University "Magna Græcia" of Catanzaro among those referred for the treatment of hyperandrogenism, obesity, metabolic alterations and/or ovarian dysfunction. The diagnosis of PCOS was based according to Rotterdam Criteria [3]. Pregnancy was ruled out by human β-chorionic gonadotropin measurement. Normal serum prolactin and normal thyroid function were established by hormonal evaluation. Late-onset non-classic congenital hyperplasia was excluded by values of basal 17-hydroxy progesterone less than 2 ng/ml [4]. Cushing syndrome was also ruled out by hormonal evaluation. Exclusionary drugs included oral contraceptive, anti-hypertensive agents, antidiabetic drugs and agents for weight loss. The purpose of the protocol was explained to the patients, and written informed consent was obtained from all patients before beginning the study. The study protocol was approved by the ethics committee of the Mater Domini Hospital Medical School of Catanzaro.

Patients were randomized into two groups by the use of randomization tables. Group A (28 patients) was given metformin (1700 mg per day) plus hypocaloric (1300 kcal) diet. Group B (28 patients) was given metformin (1700 mg per day) plus spironolactone (25 mg per day) plus hypocaloric (1300 kcal) diet. Metformin was started at a dose of 425 mg twice a day and it was increased after a week to the final dose of 850 mg twice a day. Both patient groups were treated for 6 months.

The progress of patients through the phases of the trial is shown in Fig. 1.

End points of the study included amelioration of clinical and metabolic parameters and of hyperandrogenism associated with PCOS.

The trial is registered with Clinicaltrial.gov, number NCT01526616.

### Clinical and laboratory measurements

Patients were studied during the mid-follicular phase of spontaneous menstrual cycles, both at baseline and at the end of the 6-month treatment period. Clinical history, age, anthropometric parameters (height, weight, waist circumference and BMI), menstrual cycles' characteristics (considering as normal a number equal or superior to 8 per year), Hirsutism Score (HS) [5] obtained through the Ferriman—Gallway score modification by Hatch et al., after abstention from depilation for three months (both before and after treatment) were obtained for all patients. Patients were classified into overweight (BMI 25—29.9) and obese (BMI $\geq$ 30) [6]. Patients with a waist circumference $\geq$80 cm were considered to be affected by central obesity [6].

Laboratory investigations included glycemia, lipid profile, blood count, coagulation parameters, and hepatic and renal function indexes. Hyperandrogenism was evaluated by measuring total testosterone (*T*), sex hormone binding