

Comparison of the Effects of Cyproterone Compound-Spironolactone, Metformin, and Pioglitazone on Serum Levels of High Sensitivity C-Reactive Protein and Complement System in Polycystic Ovarian Syndrome: A Randomized Double-Blind Clinical Trial

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ABSTRACT

Introduction: Polycystic ovary syndrome (PCOS) is one of the most common hormonal disorders affecting women of reproductive age. Numerous studies have suggested the involvement of inflammation in the pathogenesis of PCOS. As a result, drugs with anti-inflammatory effects may offer therapeutic benefits for this condition. The standard medications used in treating PCOS include cyproterone compound (cyproterone acetate + ethinyl estradiol) combined with spironolactone, metformin, and pioglitazone. This study aimed to compare the effects of these drugs on the serum levels of inflammatory markers, including hs-CRP, C3, and C4, in women with PCOS.

Materials and methods

Ninety women with PCOS were randomly assigned to three treatment groups for 90 days as follows: Group CC-SP received cyproterone compound (cyproterone acetate 2 mg + ethinyl estradiol 35 µg) daily, along with 100 mg/day spironolactone; Group M received metformin (1500 mg/day); and Group P received pioglitazone (30 mg/day). Serum levels of hs-CRP, C3, and C4 were measured before and after treatment.

Comparisons of changes in variables between groups were performed using the ANOVA test. Additionally, covariance (ANCOVA) analysis was conducted to examine differences between groups, adjusting for confounding variables. Probability values of ≤ 0.05 were considered statistically significant.

Results

The C3, C4, and hs-CRP levels were increased in the CC-SP group while significantly decreased in the pioglitazone group ($p < 0.05$). These changes were not statistically significant in the metformin group.

Conclusions

Pioglitazone reduces the serum levels of inflammatory markers and may be effectively combined with cyproterone and spironolactone in the treatment of PCOS.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, with a global prevalence of 5-10%. It is associated with a wide range of adverse

outcomes, including infertility, gestational diabetes, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disorders, and endometrial cancer (1). The etiology and pathogenesis of PCOS are multifactorial, with

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genetic and environmental factors contributing to its development. The majority of women with PCOS exhibit insulin resistance, which leads to hyperinsulinemia and hyperandrogenism (2). Inflammation has also been implicated in the pathogenesis of PCOS, with several studies suggesting that it is a low-grade chronic inflammatory disorder (3-6). Complement markers C3 and C4 play significant roles in the development of insulin resistance (7). Additionally, hs-CRP (highly sensitive C-reactive protein), a chronic inflammatory marker produced by the liver, contributes to the activation of the complement system, potentially leading to tissue damage in certain contexts (8). Furthermore, both hs-CRP and C3 are recognized as markers of cardiovascular complications in PCOS (7-9). Therefore, it is reasonable to conclude that PCOS patients could benefit from medications with potent anti-inflammatory effects.

The standard medications used in the treatment of PCOS in our country include cyproterone compound plus spironolactone (CC-S), metformin, and pioglitazone. Spironolactone, an aldosterone antagonist with aromatase activity and 5- α -reductase antagonistic properties, is commonly prescribed for these patients (10). It has been shown to reduce the Ferriman-Gallwey hirsutism score by an average of approximately 38% after six months of treatment (11). Cyproterone acetate, an androgen receptor antagonist with potent progestational effects, is another treatment option for PCOS. It blocks androgen receptors, inhibits 5- α -reductase activity, and increases the synthesis of sex hormone-binding globulin (SHBG) (12). The combination of cyproterone acetate and ethinyl estradiol is also widely used in PCOS treatment (13). Moreover, spironolactone is frequently added to the cyproterone/ethinyl estradiol (cyproterone compound) combination to enhance its anti-androgenic effects and protect patients against hyperaldosteronism (14, 15). On the other hand, it is well-established that biguanides and thiazolidinediones improve insulin sensitivity and reduce serum testosterone levels as well as hirsutism scores in PCOS patients (16, 17). A limited number of studies have compared the effects of these medications on hs-CRP levels and, particularly, on the complement system (18-20). This study aimed to evaluate and compare the effects of cyproterone compound plus spironolactone, metformin, and pioglitazone on the serum levels of C3 and C4 complements, as well as hs-CRP, in women with PCOS.

Materials and Methods

Trial design

The study was designed as a three-arm, randomized, double-blind clinical trial with a parallel 1:1:1 allocation ratio, and no changes were made to the methodology after the commencement of the trial.

Participants

Ninety-eight women aged 18 to 35 years, who were referred to an endocrinologist at Shahid Motahari Clinic of Shiraz University of Medical Sciences, Iran, were evaluated for inclusion in this clinical trial. The inclusion criteria were based on the 2003 Rotterdam criteria (21): and required the presence of at least two of the following: 1. Oligo-ovulation or anovulation; 2. Clinical and/or biochemical signs of hyperandrogenism; 3. Polycystic ovaries, as determined by ultrasonography. Exclusion criteria included other hyperandrogenic conditions such as 21-hydroxylase-deficient nonclassic adrenal hyperplasia, thyroid disorders, hyperprolactinemia, androgen-producing tumors, drug-induced androgen excess, syndromes of severe insulin resistance, Cushing's syndrome, and glucocorticoid resistance.

The exclusion criteria were as follows: smoking, pregnancy, diabetes mellitus, renal dysfunction (serum creatinine >1.5 mg/dl), congenital adrenal hyperplasia, unexplained serum alanine aminotransferase (ALT) elevation greater than 2.5 times the normal range, thyroid dysfunction, systemic or febrile illnesses, malignancy, use of sex hormone therapy or antiandrogens within three months prior to the study, and a history of glucocorticoid or anti-inflammatory drug use within six months before the survey.

Interventions

Patients were randomly assigned to three parallel groups with equal numbers and received the following treatments for 90 days: cyproterone compound (cyproterone acetate 2 mg plus ethinyl estradiol 35 μ g) (Aburaihan Company, Iran) daily, combined with spironolactone 50 mg (Iran Hormone Company, Iran) twice daily; metformin 500 mg (Chemidarou Company, Iran) three times daily; and pioglitazone 30 mg (Daroupakhsh Company, Iran) daily. During the study period, patients were also advised to avoid using other medications, including hormonal agents, steroids, antioxidants, and vitamin supplements. The clinic physician regularly followed up on them. The patients completed A medication prescription form

for each dose, and the clinic secretary maintained close contact with the patients to ensure proper medication adherence.

Assessments

At the initial visit, demographic data, including age, height, weight, and BMI (body mass index), were recorded for each patient. After 12 hours of fasting, a 15 ml blood sample was collected from each patient to assay the following index: C3, C4, hs-CRP, LH (luteinizing hormone), FSH (follicle-stimulating hormone), total testosterone, free testosterone, SHBG (sex hormone-binding globulin), DHEAS (dehydroepiandrosterone sulfate), estradiol, prolactin, FBS (fasting blood sugar), and insulin. These measurements were repeated at the end of the study. All blood samples were collected during the 2nd or 3rd day of the menstrual cycle. The blood samples were centrifuged at 4000 rpm for 10 minutes, and the sera were separated and stored at -80°C until analysis.

Complement levels of C3 and C4 were measured using the immunonephelometric method with Minineph™ Human C3 and C4 kits (Binding Site Group Ltd, 8 Calthorpe, UK). hs-CRP was also measured using the immunonephelometric method with a Dade-Behring BNII nephelometer (Siemens Healthcare GmbH, Germany).

Height and weight were measured using a stadiometer and standard weighing scale. BMI was calculated as weight in kilograms divided by the square of height in meters. Hirsutism scores were calculated for each patient based on the Ferriman-Gallwey scoring system (22).

LH and FSH levels were measured using the IRMA method with standard kits (Padtan Gostar Isar Company, Iran). Total testosterone was measured using the Radioimmunoassay (RIA) method (TESTO-CT2 Cisbio Bioassay kit, France). Free testosterone was measured using the ELISA method (Accu-Bind ELISA Microwells kit, USA). SHBG was measured using the Electrochemiluminescence Immunoassay (ECLIA) method (Roche Diagnostics Corporation kit, Germany). DHEAS was measured using the RIA method (DHEA-SO4 [125] RIA kit, Budapest). Estradiol was measured using the ELISA method (Azmaplast Company, Iran). Prolactin levels were measured using the IRMA method (Human Prolactin IRMA kit, Padtan Gostar Isar Company, Iran). FBS was assessed using the enzymatic colorimetric method with standard kits (Pars Azmun Company, Iran). Serum insulin levels were measured using the immunoradiometric assay

(IRMA) method (Izotop Company, Hungary). Insulin resistance was assessed by calculating the HOMA-IR index using the following equation: $\text{fasting insulin } (\mu\text{IU/mL}) \times \text{fasting glucose } (\text{mg/dL}) / 405$.

Randomization and Masking Methods

Ninety patients were randomized into three equal parallel groups by the clinic secretary, who was instructed to use the block randomization method with a randomized list generated using Microsoft Excel. The researchers and statisticians were blinded to the group allocations. However, the patients were not blinded to the treatment due to differences in the prescribed dosages.

Statistical analysis

All data were analyzed using SPSS Version 23. The normality of the data was assessed using the Shapiro-Wilk test. Data are presented as means $\pm$ SD. Probability values ≤ 0.05 were considered statistically significant. An intention-to-treat analysis was performed. Analysis of baseline clinical and biochemical parameters was conducted using analysis of variance (ANOVA). A paired sample t-test was used to compare the differences in variables before and after treatment within each group. Comparisons of the changes in variables (post-treatment vs. pre-treatment) between groups were performed using the ANOVA test. Additionally, covariance (ANCOVA) analysis was applied to analyze the differences between groups, adjusting for confounding variables such as age, weight, BMI, and HOMA-IR.

Sample size estimation

The sample size was calculated by a statistician using PASS 11 (2011) software, based on a previous study (23). Considering a two-sided significance level of 0.05, a power of 0.80, an expected effect size of 0.5 for hs-CRP, and a 20% estimated dropout rate, the required sample size was determined to be 24 participants per group.

Ethical considerations

The study protocol complied with the Declaration of Helsinki and was approved by the Local Ethics Committee of Shiraz University of Medical Sciences (Reference No.: CT-P-9145-4025). The study was registered in the Clinical Trials Registry (ClinicalTrials.gov ID: NCT02689843). All patients were informed about the study protocol and the medications' effects and potential side effects. Each patient provided written informed consent.

Results

Baseline characteristics

From February 2018 to August 2018, ninety-eight patients who met the inclusion criteria were screened, of whom 90 were randomized. Eleven patients (six from the CC-SP group, three from the metformin (M) group, and two from the pioglitazone (P) group) were lost to follow-up and did not return

for outcome measurements. Seventy-nine patients completed the 3-month medication regimen. There were no significant differences in anthropometric, clinical, or biochemical parameters between the three groups before the start of treatment ([Table 1](#)).

Table 1. The anthropometric, clinical and biochemical characteristics of patients with polycystic ovarian syndrome (PCOS) allocated in different treatment groups before treatment

Variables	CC-SP	Metformin	Pioglitazone	P value
Age (years)	20.29±0.25	20.85±0.36	20.32±0.45	0.83
Weight (Kg)	58.83±0.16	66.76±0.32	64.32±0.23	0.16
BMI (kg/m ²)	23.18±0.41	25.40±0.70	24.90±0.20	0.29
Waist circumference (cm)	75.96±0.46	81.26±0.39	80.79±0.25	0.36
Hip circumference (cm)	95.54±0.60	100.44±0.90	99.32±0.95	0.29
Hirsutism score	22.86±0.37	20.22±0.50	21.65±0.11	0.29
C3 (IU/L)	1.60±0.29	1.53±0.40	1.70±0.35	0.24
C4 (IU/L)	0.33±0.09	0.31±0.10	0.34±0.10	0.47
hs-CRP (mg/L)	1.03±0.08	1.19±0.31	1.23±0.25	0.83
LH (mIU/mL)	16.56±0.50	22.79±0.19	17.55±0.20	0.23
FSH (mIU/mL)	5.20±0.80	5.95±0.15	5.48±0.50	0.55
LH/FSH ratio	3.68±0.10	3.74±0.80	3.37±0.20	0.83
Total testosterone (ng/mL)	1.25±0.62	1.03±0.47	1.03±0.49	0.24
Free testosterone (pg/mL)	6.26±0.77	4.69±0.69	4.34±0.79	0.22
SHBG (nmol/L)	30.39±0.05	31.55±0.60	29.21±0.60	0.91
DHEAS (pg/mL)	3.70±0.39	3.04±0.55	2.86±0.56	0.12
Estradiol (pg/mL)	100.30±0.70	74.21±0.80	99.36±0.60	0.55
Prolactin (ng/mL)	11.65±0.85	13.35±0.63	9.24±0.59	0.10
FBS (mg/dL)	82.08±0.80	85.07±0.60	81.43±0.10	0.54
Insulin (μIU/mL)	9.44±0.09	13.50±0.18	10.37±0.29	0.88
HOMA-IR	2.02±0.01	2.94±0.80	2.08±0.36	0.11

All values are expressed as mean±SEM (one-way ANOVA followed by Tukey's test). *p* values ≤ 0.05 were considered statistically significant.

BMI: Body mass index; CC-SP: Cyproterone compound plus spironolactone; DHEAS: Dehydroepiandrosterone sulfate; FBS: Fasting blood sugar; FSH: Follicle-stimulating hormone; HOMA-IR: Homeostatic model assessment for insulin resistance; hs-CRP: High-sensitivity C-reactive protein; LH: Luteinizing hormone; SHBG:

Sex hormone binding globulin

Inflammatory markers

Table 2 shows the values of the variables in the

intervention groups before and after treatment. ([table2](#)).

Comparison of pre- and post-treatment data revealed that C3, C4, and hs-CRP levels were significantly decreased in the pioglitazone group (*p*<0.05). These markers increased significantly in the CC-SP group (*p*<0.05) and remained almost unchanged in the metformin group. Data analysis using one-way ANOVA showed significant differences in the changes of mean serum C3, C4, and hs-CRP levels between groups (*p*<0.05) ([Figure 1](#)).

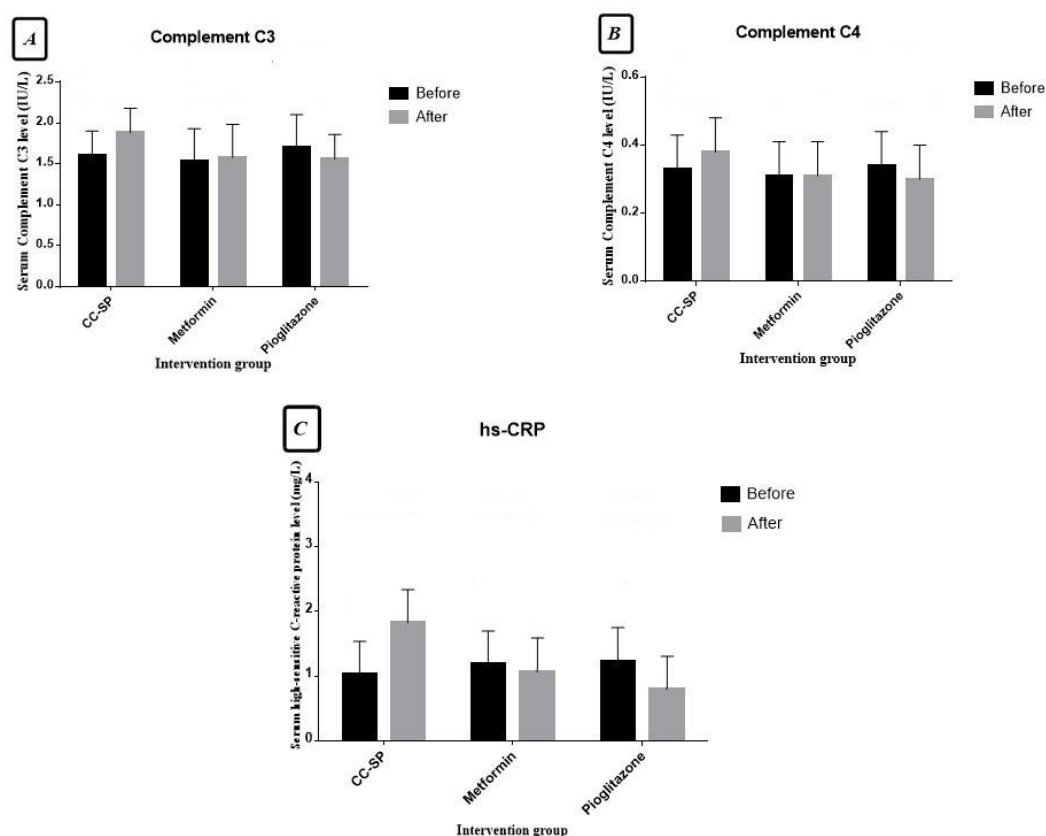


Table 2. Comparison of the anthropometric, clinical and biochemical variables of patients with polycystic ovarian syndrome (PCOS) before and after treatment with cyproterone compound- spironolactone, metformin or pioglitazone

Variables	CC-SP		Metformin		Pioglitazone		P values		
	Before	After	Before	After	Before	After	CC-SP vs. Metformin	CC-SP vs. Pioglitazone	Metformin vs. Pioglitazone
Weight (Kg)	58.83±0.16	57.67±0.13	66.76±0.32	65.56±0.24	64.32±0.23	65.63±0.43	0.96	0.001	0.001
BMI (kg/m ²)	23.18±0.41	22.72±0.50	25.40±0.70	24.92±0.50	24.90±0.20	25.39±0.25	0.93	0.001	0.001
Waist circumference (cm)	75.96±0.46	74.13±0.30	81.26±0.39	80.70±0.34	80.79±0.25	78.89±0.30	0.64	0.97	0.60
Hip circumference (cm)	95.54±0.60	93.8±0.80	100.44±0.90	98.07±0.88	99.32±0.95	98.93±0.50	0.61	0.30	0.11
Hirsutism score	22.86±0.37	20.95±0.50	20.22±0.50	19.67±0.30	21.65±0.11	20.73±0.50	0.06	0.18	0.59
C3 (IU/L)	1.60±0.29	1.88±0.30	1.53±0.40	1.58±0.40	1.70±0.35	1.56±0.30	0.02	0.0001	0.04
C4 (IU/L)	0.33±0.09	0.38±0.10	0.31±0.10	0.31±0.10	0.34±0.10	0.30±0.10	0.05	0.0001	0.06
hs-CRP (mg/L)	1.03±0.08	1.83±0.50	1.19±0.31	1.07±0.40	1.23±0.25	0.80±0.10	0.0001	0.0001	0.19
LH (mIU/mL)	16.56±0.50	6.35±0.60	22.79±0.19	23.92±0.50	17.55±0.20	17.27±0.40	0.008	0.02	0.72
FSH (mIU/mL)	5.20±0.80	2.90±0.83	5.95±0.15	5.19±0.18	5.48±0.50	5.83±0.30	0.06	0.002	0.16
LH/FSH ratio	3.68±0.10	2.61±0.30	3.74±0.80	4.78±0.80	3.37±0.20	3.19±0.70	0.01	0.29	0.14

Total testosterone (ng/mL)	1.25±0.62	0.94±0.70	1.03±0.47	0.91±0.20	1.03±0.49	0.99±0.40	0.13	0.03	0.52
Free testosterone (pg/mL)	6.26±0.77	3.33±0.80	4.69±0.69	4.75±0.20	4.34±0.79	4.88±0.40	0.0001	0.0001	0.48
SHBG (nmol/L)	30.39±0.05	150.25±0.09	31.55±0.60	29.39±0.80	29.21±0.60	41.35±0.20	0.0001	0.0001	0.16
DHEAS (pg/mL)	3.70±0.39	3.24±0.50	3.04±0.55	3.41±0.80	2.86±0.56	2.43±0.10	0.005	0.93	0.005
Estradiol (pg/mL)	100.30±0.70	27.08±0.20	74.21±0.80	93.21±0.40	99.36±0.60	99.50±0.60	0.004	0.02	0.54
Prolactin (ng/mL)	11.65±0.85	11.58±0.72	13.35±0.63	13.52±0.80	9.24±0.59	10.36±0.10	0.89	0.51	0.58
FBS (mg/dL)	82.08±0.80	78.67±0.60	85.07±0.60	81.48±0.55	81.43±0.10	81.18±0.80	0.96	0.38	0.34
Insulin (μU/mL)	9.44±0.09	11.29±0.05	13.50±0.18	13.78±0.13	10.37±0.29	11.10±0.50	0.46	0.59	0.82
HOMA-IR	2.02±0.01	2.18±0.04	2.94±0.80	2.88±0.60	2.08±0.36	2.23±0.10	0.69	0.99	0.69

After adjusting for age, weight, and HOMA-IR as confounding factors, the differences between groups in inflammatory markers remained significant ($p=0.0001$ for C3, $p=0.003$ for C4, and $p=0.0001$ for hs-CRP).

Hormonal changes

Comparison of the groups using one-way ANOVA showed significant differences in the serum levels of LH, FSH, total testosterone, free testosterone, estradiol, insulin, and SHBG after 90 days of drug treatment ($p<0.05$). It was found that while serum levels of LH, FSH, total testosterone, free testosterone, and estradiol significantly decreased in the CC-SP group, insulin levels and SHBG significantly increased ($p<0.05$). In the metformin group, no hormonal changes were statistically significant. However, in the pioglitazone group, significant increases in SHBG and decreases in DHEAS levels were observed ($p<0.05$). The other hormonal indices did not change significantly after treatment with pioglitazone.

Adverse events

Two patients in the metformin group developed gastrointestinal side effects, and one patient in the pioglitazone group developed mild lower extremity edema. However, all patients continued their medications throughout the study.

All values are expressed as mean±SEM. For comparison of the differences of the variables before and after treatment in each group, the paired sample t test was used. Comparisons of the changes in variables (after -before) between groups were performed with one-way ANOVA followed by Tukey's test. p values ≤ 0.05 were considered statistically significant.

BMI: Body mass index; CC_SP: Cyproterone compound plus spironolactone; DHEAS: Dehydroepiandrosterone sulfate; FBS: Fasting blood sugar; FSH: Follicle-stimulating hormone; HOMA-IR: Homeostatic model assessment for insulin resistance; hs-CRP: High-sensitivity C-reactive protein; LH: Luteinizing hormone; SHBG: Sex hormone binding globulin

Discussion

The role of inflammation in the pathogenesis of PCOS has been demonstrated in numerous studies. A meta-analysis of thirty-one articles meeting the inclusion criteria for PCOS reported elevated hs-CRP levels in these patients (3). A strong association between the complement system and insulin resistance, which is commonly observed in PCOS, has also been suggested (24). Additionally, several studies have proposed a correlation between hs-CRP and C3 as well as C4 (25, 26). In this study, we found that pioglitazone decreased the serum levels of C3, C4, and hs-CRP, whereas metformin showed no change, and the combination of cyproterone and spironolactone increased the concentrations of these inflammatory markers. Our findings regarding the effects of pioglitazone on hs-CRP are consistent with the results of other clinical trials (27). A clinical trial reported that treatment of PCOS patients with ethinyl estradiol/drospirenone (which has effects similar to cyproterone compound) plus spironolactone significantly increased hs-CRP levels (28). Furthermore, in line with our findings, Aghamohammadzadeh et al. reported no beneficial effect of metformin on hs-CRP after treating PCOS patients with this drug (18).

Overall, based on the results of this study, pioglitazone appears to be the most effective drug for reducing inflammation in patients with PCOS. However, pioglitazone does not address all metabolic and hormonal abnormalities associated with this condition. Therefore, we suggest using pioglitazone as an adjunct to other medications, such as the combination of cyproterone compound and spironolactone.

Our study had both strengths and limitations. A key strength was the comparison of the effects of routine medications used to treat PCOS on serum levels of C3, C4, and hs-CRP. The limitations of our study included the relatively small sample size and the short duration of treatment. Further clinical trials with larger sample sizes and more prolonged treatment durations, targeting other inflammatory markers, are needed. Additionally, it is crucial to design further research to explore the mechanisms of inflammation in the pathogenesis of PCOS to develop new drugs with combined anti-androgenic and anti-inflammatory properties.

Conclusion

This randomized clinical trial demonstrated that pioglitazone benefits the serum levels of inflammatory markers C3, C4, and hs-CRP. It can be used as an adjunct to other drugs, such as the combination of cyproterone and spironolactone, in the treatment of PCOS patients.

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Statement of Ethics

The study protocol complied with the Declaration of Helsinki and was approved by the Local Ethics Committee of Shiraz University of Medical Sciences (Reference No.: CT-P-9145-4025). The study was registered in the Clinical Trials Registry (ClinicalTrials.gov ID: NCT02689843). The patients were informed about the research protocol and the medications' effects and side effects. Each patient gave a written informed consent.

Conflict of Interest

The authors have no conflicts of interest to declare.

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References

1. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clin Epidemiol*. 2013;6:1-13. doi:10.2147/CLEP.S37559 [PMid:24379699]
2. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. *Nat Rev Endocrinol*. 2011;7(4):219-31. doi:10.1038/nrendo.2010.217 [PMid:21263450]
3. Escobar-Morreale HF, Luque-Ramírez M, González F. Circulating inflammatory markers in polycystic ovary syndrome: a systematic review and metaanalysis. *Fertil Steril*. 2011;95(3):1048-58.e1-2. doi:10.1016/j.fertnstert.2010.11.036 [PMid:21168133]
4. Samy N, Hashim M, Sayed M, Said M. Clinical significance of inflammatory markers in polycystic ovary syndrome: their relationship to insulin resistance and body mass index. *Dis Markers*. 2009;26(4):163-70. doi:10.1155/2009/465203 [PMid:19729797]
5. Duleba AJ, Dokras A. Is PCOS an inflammatory process? *Fertil Steril*. 2012;97(1):7-12. doi:10.1016/j.fertnstert.2011.11.023 [PMid:22192135]
6. Benson S, Janssen OE, Hahn S, Tan S, Dietz T, Mann K, et al. Obesity, depression, and chronic low-grade inflammation in women with polycystic ovary syndrome. *Brain Behav Immun*. 2008;22(2):177-84. doi:10.1016/j.bbi.2007.07.003 [PMid:17716857]
7. Snyder ML, Shields KJ, Korytkowski MT, Sutton-Tyrrell K, Talbott EO. Complement protein C3 and coronary artery calcium in middle-aged women with polycystic ovary syndrome and controls. *Gynecol Endocrinol*. 2014;30(7):511-5. doi:10.3109/09513590.2014.895985 [PMid:24592986]
8. Griselli M, Herbert J, Hutchinson WL, Taylor KM, Sohail M, Krausz T, et al. C-reactive protein and complement are important mediators of tissue damage in acute myocardial infarction. *J Exp Med*. 1999;190(12):1733-40. doi:10.1084/jem.190.12.1733 [PMid:10601349]
9. Tarkun I, Arslan BC, Cantürk Z, Türemen E, Sahin T, Duman C. Endothelial dysfunction in young women with polycystic ovary syndrome: relationship with insulin resistance and low-grade chronic inflammation. *J Clin Endocrinol Metab*. 2004;89(11):5592-6. doi:10.1210/jc.2004-0751 [PMid:15531516]
10. Sabbadin C, Andrisani A, Zermiani M, Donà G, Bordin L, Ragazzi E, et al. Spironolactone and intermenstrual bleeding in polycystic ovary syndrome with normal BMI. *J Endocrinol Invest*. 2016;39(9):1015-21. doi:10.1007/s40618-016-0466-0 [PMid:27072668]
11. Lobo RA, Shoupe D, Serafini P, Brinton D, Horton R. The effects of two doses of spironolactone on serum androgens and anagen hair in hirsute women. *Fertil Steril*. 1985;43(2):200-5. doi:10.1016/S0015-0282(16)48373-1 [PMid:3967781]
12. Mowszowicz I, Wright F, Vincens M, Rigaud C, Nahoul K, Mavrić P, et al. Androgen metabolism in hirsute patients treated with cyproterone acetate. *J Steroid Biochem*. 1984;20(3):757-61. doi:10.1016/0022-4731(84)90081-5 [PMid:6231428]
13. Taheripana R, Sepahvandi M, Entezari A, Amiri Z, Samani EN. Evaluation of serum PSA after cyproterone compound treatment compared with oral contraceptive pill in hirsute polycystic ovary syndrome patients. *Middle East Fertility Society Journal*. 2010;15(3):159-62. doi:10.1016/j.mefs.2010.06.007
14. Armanini D, Bordin L, Donà G, Sabbadin C, Bakdounes L,

- Ragazzi E, et al. Polycystic ovary syndrome: Implications of measurement of plasma aldosterone, renin activity and progesterone. *Steroids*. 2012;77(6):655-8. doi:10.1016/j.steroids.2012.02.010 [PMid:22387621]
15. Zulian E, Sartorato P, Benedini S, Baro G, Armanini D, Mantero F, et al. Spironolactone in the treatment of polycystic ovary syndrome: effects on clinical features, insulin sensitivity and lipid profile. *J Endocrinol Invest*. 2005;28(1):49-53. doi:10.1007/BF03345529 [PMid:15816371]
16. Motta AB. Mechanisms involved in metformin action in the treatment of polycystic ovary syndrome. *Curr Pharm Des*. 2009;15(26):3074-7. doi:10.2174/138161209789058101 [PMid:19754381]
17. Froment P, Touraine P. Thiazolidinediones and Fertility in Polycystic Ovary Syndrome (PCOS). *PPAR Res*. 2006;2006:73986. doi:10.1155/PPAR/2006/73986 [PMid:17347533]
18. Aghamohammadzadeh N, Aliasgarzadeh A, Baglar L, Abdollahifard S, Bahrani A, Najafipour F, et al. Comparison of metformin and cyproteroneestrodial compound effect on hs c-reactive protein and serum androgen levels in patients with poly cystic ovary syndrome. *Pakistan Journal of Medical Sciences Online*. 2010;26:347-51.
19. Dardzińska JA, Rachoń D, Kuligowska-Jakubowska M, Aleksandrowicz-Wrona E, Płoszyński A, Wyrzykowski B, et al. Effects of metformin or an oral contraceptive containing cyproterone acetate on serum c-reactive protein, interleukin-6 and soluble vascular cell adhesion molecule-1 concentrations in women with polycystic ovary syndrome. *Exp Clin Endocrinol Diabetes*. 2014;122(2):118-25. doi:10.1055/s-0033-1363261 [PMid:24554512]
20. Shahebrahimi K, Jalilian N, Bazgir N, Rezaei M. Comparison clinical and metabolic effects of metformin and pioglitazone in polycystic ovary syndrome. *Indian J Endocrinol Metab*. 2016;20(6):805-9. doi:10.4103/2230-8210.192925 [PMid:27867884]
21. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril*. 2004;81(1):19-25. doi:10.1016/j.fertnstert.2003.10.004 [PMid:14711538]
22. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab*. 1961;21:1440-7. doi:10.1210/jcem-21-11-1440 [PMid:13892577]
23. Stabile G, Borrielli I, Arsenio AC, Bruno LM, Benvenega S, Giunta L, et al. Effects of the insulin sensitizer pioglitazone on menstrual irregularity, insulin resistance and hyperandrogenism in young women with polycystic ovary syndrome. *J Pediatr Adolesc Gynecol*. 2014;27(3):177-82. doi:10.1016/j.jpog.2013.09.015 [PMid:24814528]
24. Yang S, Li Q, Song Y, Tian B, Cheng Q, Qing H, et al. Serum complement C3 has a stronger association with insulin resistance than high-sensitivity C-reactive protein in women with polycystic ovary syndrome. *Fertil Steril*. 2011;95(5):1749-53. doi:10.1016/j.fertnstert.2011.01.136 [PMid:21316661]
25. Karkhaneh M, Qorbani M, Mohajeri-Tehrani MR, Hoseini S. Association of serum complement C3 with metabolic syndrome components in normal weight obese women. *J Diabetes Metab Disord*. 2017;16:49. doi:10.1186/s40200-017-0330-6 [PMid:29299442]
26. Jovicić S, Ignjatović S, Dajak M, Kangrga R, Majkić-Singh N. Association of lipid and inflammatory markers with C-reactive protein in cardiovascular risk assessment for primary prevention. *Clin Lab*. 2009;55(11-12):411-9.
27. Szapary PO, Bloedon LT, Samaha FF, Duffy D, Wolfe ML, Soffer D, et al. Effects of pioglitazone on lipoproteins, inflammatory markers, and adipokines in nondiabetic patients with metabolic syndrome. *Arterioscler Thromb Vasc Biol*. 2006;26(1):182-8. doi:10.1161/01.ATV.0000195790.24531.4f [PMid:16284192]
28. Harmanci A, Cinar N, Bayraktar M, Yildiz BO. Oral contraceptive plus antiandrogen therapy and cardiometabolic risk in polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2013;78(1):120-5. doi:10.1111/j.1365-2265.2012.04466.x [PMid:22702394]