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Beneficial effects of pioglitazone and α-lipoic acid in patients with polycystic ovaries syndrome

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Abstract. – OBJECTIVE: Changes in hormone levels, improper lipid metabolism, and oxidative stress all significantly contribute to the pathogenic process of polycystic ovarian syndrome (PCOS). According to earlier research, pioglitazone and alpha-lipoic acid are crucial in the emergence of PCOS. The beneficial effects of pioglitazone and alpha-lipoic acid on PCOS were examined in the current study.

PATIENTS AND METHODS: The 120 patients with PCOS received three months of treatment in pioglitazone groups (n=40 case, 30 mg/time, 1 time/day), α-lipoic acid (n=40 case, 0.6 g/time, 1 time/day), and combination therapy (n=40 case, pioglitazone 30 mg/time, 1 time/day and α-lipoic acid, 0.6 g/time, 1 time/day). Before and after therapy, the following factors were evaluated: the hormonal profile, fasting serum insulin, body weight, body mass index (BMI), menstruation status, oxidative stress, and indications of lipid metabolism.

RESULTS: The combination of pioglitazone and α-lipoic acid has a significantly improving effect on BMI, body weight, oxidative stress levels, lipid metabolism, and menstrual status. A significant increase in body weight, BMI, and follicle-stimulating hormone (FSH) levels were found in mice after being treated with α-lipoic acid alone. However, the use pioglitazone alone improves body weight, BMI, the calculation of insulin resistance index (HOMA-IR), Area under the curve (AUC)-insulin, fasting glucose/insulin (G/I) ratio, total testosterone, and malondialdehyde (MDA) levels in post-treatment than pre-treatment.

CONCLUSIONS: These findings suggest that pioglitazone alone has a better effect than alpha-lipoic acid in improving oxidative stress levels, BMI, and menstrual cyclicity. Additionally, treatment with pioglitazone and alpha-lipoic acid did demonstrate a greater effect than monotherapy with each medication alone.

Key Words:
α-lipoic acid, Oxidative stress, Pioglitazone, Polycystic ovary syndrome.

Introduction

With a frequency of up to 6% to 10% in women of childbearing age, polycystic ovarian syndrome (PCOS) is a prevalent endocrine illness linked to reproductive and metabolic diseases in women and a significant contributor to infertility[1]. Patients are mainly manifested as hyperandrogenemia, menstrual thinning, anovulation, and ovarian polycystic changes, and some patients also have insulin resistance and dyslipidemia, which have a significant negative impact on women's physical and emotional health, and quality of life[2]. If PCOS is not corrected in time, it additionally raises the chance of illnesses including endometrial cancer, type 2 diabetes, cardiovascular disease, and metabolic syndrome. However, due to the diversification of the clinical manifestations of PCOS, the complexity of the etiology, and the pathogenesis is not yet clear, there is no effective cure for PCOS at present, and the clinical treatment is mainly symptomatic, including anti-estrogen, gonadotropin, surgical treatment, and other measures, but because of its highly heterogeneous clinical manifestations, the clinical efficacy is not obvious. Therefore, there is an urgent need for new ideas and solutions to prevent PCOS[3].

An oxidative/antioxidant imbalance brought on by the body's excessive generation of reactive oxygen species that exceeds its intrinsic antiox-

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idant defense level is known as oxidative stress (OS)[4]. When the balance between the body's oxidative substances and antioxidant systems is disturbed and tends to the former, reactive oxygen species (ROS) increase and accumulate in the body, causing oxidative damage to DNA, proteins, and lipids in cells and affecting cell function, inducing various diseases. Oxidative stress, which is an imbalance of oxidants and antioxidants in the body, is crucial to the pathological and physiological processes of many illnesses. So far, research in both animal and human reproductive medicine has focused heavily on the connection between oxidative stress and PCOS. Studies[5] have suggested that there is also a dynamic balance of oxidation and antioxidant in the follicle microenvironment of the ovaries, and this dynamic balance is closely related to the maturity of the follicle: the high concentration of enzymatic antioxidants such as superoxide dismutase (SOD), catalase, etc. in the follicle fluid, and the high concentration of non-enzymatic antioxidants.

Lipoic acid is a natural antioxidant, with a unique redox two-way function of powerful antioxidant inhibitors, which can activate a variety of antioxidant metabolic cycles, reduce the antioxidant system in the human body, scavenge intracellular oxygen free radicals, and play a powerful biological antioxidant effect[6]. Lipoic acid was discovered in potatoes in 1937, and in 1951, Reed et al[7] isolated 30 mg from 10 tons of bovine liver and named it lipoic acid. Studies have found[8] that it is a highly active antioxidant, so its antioxidant effects have attracted much attention. Some animal experiments and clinical applications[9] have shown that lipoic acid can increase the reduced glutathione content in serum or tissue homogenate, reduce malondialdehyde levels, produce direct protective effects on the attack of free radicals on islet cells, reduce oxidative stress, and can be used to prevent and treat a variety of diseases, such as diabetes, Alzheimer's disease, aging, cardiovascular disease, showing a wide range of application prospects in medicine, health food, cosmetics, and other fields. Lipoic acid is widely used in health applications in the United States and Europe, and Japan and widely used in the food and pharmaceutical fields[10]. In China, there has been more research[11] on lipoic acid since 2006. However, at present, there are few clinical studies[12] locally and abroad on the application of lipoic acid to patients with polycystic ovary syndrome.

Thiazolidinediones (pioglitazone) are a class of insulin sensitizers, their main mechanism is to increase insulin sensitivity, with highly selective agonist peroxidase small growth factor activation receptors, and then regulate the transcription of a variety of insulin genes related to lipid metabolism and glucose metabolism, thereby inhibiting insulin resistance in peripheral cells and improving metabolism[13]. At present, it is a first-line drug for the clinical diagnosis and treatment of PCOS patients with insulin resistance and hyperinsulinemia[14].

The purpose of this study was to analyze whether alpha-lipoic acid (ALA) and pioglitazone could improve PCOS symptoms by improving insulin resistance and oxidative stress levels, and consequently, PCOS symptoms. This provides new ideas and clinical treatments for the treatment of PCOS.

Patients and Methods

This research is a single-center, controlled, randomized, and blinded trial. The Xuzhou First People's Hospital's Ethical Committee and the Institutional Review Board both gave their approval for this study. All patients completed an informed consent form after receiving information. These studies adhere to the Declaration of Helsinki as well as the CONSORT recommendations, and the clinical study was registered at our hospital (xznss-232123, clinical trial number: 2585841-14).

Subjects

120 PCOS patients treated at the Xuzhou First People's Hospital's Endocrinology or Gynecology Departments between January 2021 and June 2021 were chosen for the study. Their ages ranged from 18 to 30. Inclusion criteria: (1) Meet the PCOS diagnostic criteria, that are: persistent anovulation, sparse ovulation, hyperandrogenemia, and the presence of ovarian polycystic changes, that are unilateral and bilateral ovarian follicles with a diameter of 2 to 9 mm, the number of follicles ≥12, and the volume of the ovaries ≥10mL according to the Rotterdam criteria[15]. The diagnosis of PCOS was based on at least two of the three following abnormalities according to the 2003 Rotterdam Consensus Conference[15]: 1) oligomenorrhoea or amenorrhea; oligomenorrhea was defined as a menstrual cycle with an interval of ≥35 days. Secondary amenorrhea was defined as the absence of menses for at least six months.

Irregular menstrual cycles were defined as a cycle with changes in the intermenstrual interval of more than ±4 days and a period of ≤35 days. Regular menstrual cycle was defined as cycles with a minimum and maximum length change of fewer than four days and cycle length ranging from 21-35 days; 2) manifestation of hyperandrogenemia such as hirsutism (Ferriman-Gallwey Score ≥8), acne, and/or serum total testosterone greater than 70 ng/dL; 3) polycystic ovaries diagnosis is based on ultrasonography; confirmed by the presence of 12 or more subcapsular follicles measuring 2-9 mm in diameter at least in one ovary or increased ovarian volume (>10 cm^3). (2) Sign the informed consent form voluntarily. Exclusion criteria: (1) hyperandrogenemia caused by congenital adrenal hyperplasia or tumor secretion androgen; (2) concomitant thyroid diseases; (3) hypersensitivity to the use of drugs in this study; (4) have recently used sex hormones and antipsychotic drugs; (5) cognitive impairment; (6) patients with severe heart, liver, and kidney diseases.

Study Design

This study was a randomized controlled study, using a random number table method to randomly divide patients into three groups such as pioglitazone group, lipoic acid group, and combination group. Patients in the pioglitazone group were given pioglitazone treatment, orally, 30 mg/time, 1 time/day; the lipoic acid group was given lipoic acid treatment, oral, 0.6 g/time, 1 time/day; patients in the experimental group based on control group treatment combined with lipoic acid therapy, oral, 0.6 g/time, 1 time/day. The combination group was treated continuously for 3 months.

Laboratory Assay

Blood pressure and body mass index were measured in all subjects before and after treatment and 5 mL of venous blood were collected from three groups of patients, centrifuged at a rotational speed of 3,000 r/min for 15 min, separated to obtain serum, and placed in a -80°C refrigerator for backup. The following indicators before and after treatment were detected and compared in the three groups: (1) sex hormone-related indicators, including follicle-stimulating hormone (FSH), Luteotropic hormone (LH), Dehydroepiandrosterone sulfate (DHEAS), testosterone (T), all detected by immunometric assays (Johnson & Johnson S.p.A-Ortho Clinical Inc., Rochester, NY, USA). The intra-assay and inter-assay coefficients of variability (CV) for the FSH, LH, DHEAS, and testosterone assay were 4.8-5.8% and 4.8-8.0%, 6.3-7.9%, and 3.4-4.9%, 2.8-3.6%, and 5.8-6.9%, 2.1%-3.9% and 4.8-7.1% respectively. The islet function-related indicators, including fasting serum insulin (FINS), and fasting plasma glucose (FPG) were detected by a Hitachi 7180 Biochemical Automated Analyzer (Hitachi High-Technologies Co. Shanghai, China). The calculation of insulin resistance index (HOMA-IR) is based on a steady-state model with the formula of HOMA-IR=FPG×FINS/22.5. The intra-assay and inter-assay CV for the FINS and FPG assay were 2.8-3.9% and 1.2-6.3% respectively. The oxidative stress indicators include serum superoxide dismutase (SOD), malondialdehyde (MDA), advanced glycosylation end products (AGEs), NO, glutathione peroxidase (GSH-PX), superoxide dismutase/malondialdehyde ratio (SOD/MDA). The above indicators are detected by ELISA analysis (Abcam Co. Shanghai, China). The intra-assay and inter-assay CV for the NO, AGEs, GSH, and MDA assay were 2.5-3.8% and 1.8-5.8%, 3.6-4.9%, and 5.9-7.4%, 2.6-4.1% and 3.2-8.4%, 3.1-4.3% and 2.9-6.5%, respectively.

Statistical Analysis

We used a randomized clinical trial sample size calculation formula where type one (α) and type two errors (beta) were 0.05, and 0.20 (power=80%), respectively according to a previously published study[16]. In addition, Wilk-Shapiro test was performed to assess the normality of the distribution of variables. Student's two-tailed paired *t*-tests or the Wilcoxon signed-rank test were used to compare mean variables at baseline to mean values after treatment within groups. One-way ANOVA and post-hoc Bonferroni were carried out to compare means between three groups. Chi-square and Fisher's exact test were used to evaluate menstrual cycle. Using SPSS 20.0 (IBM Corp., Armonk, NY, USA), the data for this study were processed. The measurement data were presented in the form of mean standard deviation, whereas the count data were given as a number (n, %). There were statistical differences between the groups, as shown by the value $p<0.05$.

Results

As shown in the flow diagram, 120 patients completed the experiment. There were 40 cases in the pioglitazone group, 40 cases in the group lipoic acid, and 40 cases in the combination

group. The study found that both drugs had no significant side effects in patients with PCOS.

There was no statistically significant difference in BMI and mean age. In addition, the HOMA-index, and AUC insulin showed no significant difference among the three groups. Another baseline characteristic had been shown in Table I.

After 3 months, body weight and BMI were improved significantly after treatment with pioglitazone alone, lipoic acid alone, and combined pioglitazone and lipoic acid. No statistical difference in BMI was found when the three groups were compared (Table II). For glucose metabolism-related indicators, HOMA-index, Fasting G/I ratio, and area under the curve (AUC)-insulin (AUC-I) showed significant improvement after pioglitazone and combination therapy. The HOMA-index showed a significant statistical difference between the three groups when they were compared (p=0.02). There was no statistically significant difference in LDL cholesterol, HDL cholesterol, serum cholesterol, or serum triglycerides for lipid-related indicators in the pioglitazone and lipoic acid group alone, but LDL cholesterol and serum cholesterol both significantly decreased after combination therapy (p=0.01 and p=0.03, respectively). Moreover, total testosterone decreased significantly after pioglitazone treatment alone (p=0.02) and combined treatment group (p=0.01) and then serum testosterone (p=0.01), FSH (p=0.03), and LH (p=0.02) were increased significantly after combined treatment.

For oxidative stress indicators, MDA decreased significantly after pioglitazone treatment alone (p=0.02) and combined treatment (p=0.03). In addition, the NO (p=0.01) and TAC (p=0.03) decreased significantly and GSH (p=0.01) increased significantly after combined treatment.

Discussion

After three months of therapy, this study assessed the impact of pioglitazone and lipoic acid treatments on menstrual cycles and metabolic abnormalities in PCOS patients. Our findings show that both pioglitazone alone and lipoic acid alone, as well as a combination of pioglitazone and lipoic acid, have a significant improvement in weight and BMI. At the same time, for glucose metabolism, menstrual cycle, and oxidative stress indicators, pioglitazone alone and combination therapy groups showed good therapeutic effects.

The etiology of PCOS may involve insulin resistance and hyperandrogenism. In PCO model rats, previous research[17] indicated that pioglitazone therapy decreased blood anti-Müllerian hormone (AMH) levels and raised serum adiponectin levels. These results are associated with a decrease in the overall number of atretic follicles and the pace at which they form. When treating PCOS patients, meta-analysis studies[18] found that pioglitazone improved menstrual cycle and ovulation better than metformin while metformin improved BMI and

Table I. Baseline characteristics of women with PCOS.

Parameters	Pioglitazone	Alpha-lipoic acid	Combination	*p*-value
Age	28.32 ± 3.99	29.61 ± 2.66	26.69 ± 3.61	0.62
Menstrual length (days)	86 ± 24	89 ± 31	86 ± 22	0.85
BMI (kg/m^2)	27.22 ± 1.96	27.67 ± 3.68	28.66 ± 2.36	0.62
HOMA-index	6.63 ± 5.91	6.69 ± 2.86	6.96 ± 2.46	0.86
AUC-insulin (lU/mL *180 min)	14,885.36 ± 1,125.62	16,235.62 ± 2,035.62	16,521.67 ± 2,156.36	0.75
Fasting G/I ratio (mg/dL per µIU/mL)	7.58 ± 2.62	7.66 ± 4.63	7.62 ± 3.11	0.62
LDL cholesterol (mg/dl)	132.62 ± 12.65	125.93 ± 5.69	134.62 ± 6.99	0.75
HDL cholesterol (mg/dl)	52.99 ± 11.62	53.68 ± 11.96	51.88 ± 12.63	0.71
Serum cholesterol (mg/dl)	236.95 ± 26.68	241.63 ± 36.91	223.85 ± 22.36	0.75
Serum triglyceride (mg/dl)	142.63 ± 52.69	132.69 ± 36.65	136.02 ± 25.99	0.73
DHEAS (mg/l)	1.26 ± 0.36	1.37 ± 0.34	1.29 ± 0.42	0.63
Total testosterone (µg/l)	0.71 ± 0.21	0.79 ± 0.15	0.85 ± 0.03	0.64
FSH (IU/L)	5.36 ± 1.25	4.96 ± 1.65	5.36 ± 1.25	0.36
LH (IU/L)	7.15 ± 2.36	6.89 ± 1.96	6.98 ± 1.53	0.15
LH/FSH	1.66 ± 0.86	1.61 ± 0.69	1.59 ± 0.89	0.58

PCOS: Polycystic ovary syndrome; BMI: Body mass index; HOMA-index: Homeostasis Model Assessment-index; AUC: area under the curve; Fasting G/I ratio: Fasting glucose/insulin ratio; LDL: low-density lipoprotein; HDL: high-density lipoprotein; DHEAS: Dehydroepiandrosterone; FSH: Follicle-stimulating hormone; LHZ: luteinizing hormone.

Table II. Clinical characteristic and serum hormone in woman with PCOS after administration of pioglitazone and lipoic acid.

Parameters	Pioglitazone			Alpha-lipoic acid			Combination			*p*-value
	Pre-treatment	Post-treatment	*p*-value	Pre-treatment	Post-treatment	*p*-value	Pre-treatment	Post-treatment	*p*-value	
Weight (kg)	72.68 ± 12.63	70.62 ± 11.36	0.02	72.66 ± 11.26	70.61 ± 12.22	0.01	73.65 ± 13.66	70.15 ± 11.36	0.01	0.62
BMI (kg/m^2)	27.22 ± 1.96	26.92 ± 2.16	0.03	27.67 ± 3.68	26.35 ± 2.63	0.04	28.66 ± 2.36	26.36 ± 3.69	0.02	0.23
HOMA-index	2.63 ± 5.91	1.25 ± 0.36	0.03	2.69 ± 2.86	2.36 ± 0.63	0.62	2.96 ± 2.46	1.02 ± 0.36	0.01	0.02
AUC-insulin (lU/mL*180 min)	14,885.36 ± 1,125.62	6,235.62 ± 2,035.62	0.01	13,625.25 ± 115.66	11,253.62 ± 125.63	0.67	16,521.67 ± 2,156.36	6,023.36 ± 123.66	0.03	0.75
Fasting G/I ratio (mg/dL per µIU/mL)	7.58 ± 2.62	14.62 ± 2.61	0.03	7.66 ± 4.63	7.85 ± 1.36	0.63	7.62 ± 3.11	16.32 ± 2.06	0.02	0.62
LDL cholesterol (mg/dl)	132.62 ± 12.65	130.25 ± 10.96	0.62	125.93 ± 5.69	125.99 ± 3.69	0.42	134.62 ± 6.99	142.12 ± 3.69	0.01	0.75
HDL cholesterol (mg/dl)	52.99 ± 11.62	53.62 ± 12.62	0.15	53.68 ± 11.96	51.25 ± 13.01	0.15	51.88 ± 12.63	53.69 ± 10.64	0.06	0.71
Serum cholesterol (mg/dl)	236.95 ± 26.68	223.05 ± 18.66	0.25	241.63 ± 36.91	236.25 ± 11.36	0.16	223.85 ± 22.36	226.65 ± 24.61	0.03	0.75
Serum triglyceride (mg/dl)	142.63 ± 52.69	145.62 ± 25.99	0.36	132.69 ± 36.65	136.99 ± 36.58	0.68	136.02 ± 25.99	140.36 ± 24.15	0.36	0.73
DHEAS (mg/l)	1.26 ± 0.36	1.45 ± 0.63	0.63	1.37 ± 0.34	1.12 ± 0.51	0.63	1.29 ± 0.42	1.36 ± 0.45	0.08	0.63
Total testosterone (µg/l)	0.71 ± 0.21	0.62 ± 0.16	0.02	0.79 ± 0.15	0.56 ± 0.22	0.52	0.85 ± 0.03	0.72 ± 0.09	0.01	0.64
FSH (IU/L)	5.36 ± 1.25	5.52 ± 1.62	0.06	4.96 ± 1.65	5.02 ± 1.95	0.04	5.36 ± 1.25	5.63 ± 0.69	0.03	0.36
LH (IU/L)	7.15 ± 2.36	6.32 ± 2.15	0.25	6.89 ± 1.96	6.35 ± 1.02	0.36	6.98 ± 1.53	5.36 ± 1.02	0.02	0.15
LH/FSH	1.66 ± 0.86	1.26 ± 0.56	0.36	1.61 ± 0.69	1.60 ± 0.36	0.24	1.59 ± 0.89	1.02 ± 0.36	0.12	0.58
NO (µmol/L)	33.26 ± 2.65	32.69 ± 1.66	0.56	33.75 ± 2.63	32.06 ± 1.15	0.36	33.14 ± 2.08	30.28 ± 1.68	0.01	0.36
TAC (mmol/L)	836.69 ± 52.15	993.62 ± 43.81	0.36	832.99 ± 48.66	963.48 ± 48.66	0.42	826.47 ± 53.66	923.65 ± 47.11	0.03	0.02
GSH (µmol/L)	426.36 ± 25.61	456.36 ± 30.66	0.62	420.96 ± 16.32	496.62 ± 46.33	0.36	416.28 ± 36.25	523.61 ± 47.61	0.01	0.32
MDA (µmol/L)	2.89 ± 0.15	2.31 ± 0.32	0.02	2.92 ± 0.18	2.86 ± 0.26	0.86	2.99 ± 0.24	2.15 ± 0.19	0.03	0.02

PCOS: Polycystic ovary syndrome; BMI: Body mass index; HOMA-index: Homeostasis Model Assessment-index; AUC: area under the curve; Fasting G/I ratio: Fasting glucose/insulin ratio; LDL: low-density lipoprotein; HDL: high-density lipoprotein; DHEAS: Dehydroepiandrosterone; FSH: Follicle-stimulating hormone; LHZ: luteinizing hormone.

Ferriman-Gallwey scores better than pioglitazone. Pioglitazone may be a good alternative for PCOS patients who were intolerant of or ineligible for metformin treatment. All prokaryotic and eukaryotic cell types contain alpha-lipoic acid (ALA), sometimes referred to as thioctic acid. It has been demonstrated[19] that ALA, or its reduced form, dihydrolipoic acid (DHLA), acts as a biological antioxidant, metal chelator, and detoxifying agent, among other beneficial impacts on human health. It can also modify the insulin and NF-κB signaling pathways, as well as the oxidation of several antioxidants, including glutathione, and vitamins C and E. In addition to having an antioxidant impact, alpha-lipoic acid restored menstrual cyclicity in both groups, demonstrating that hyperinsulinemia had no effect on ovarian function and solely affects the metabolic response to therapy[20]. In addition, alpha-lipoic acid integrative administration at a low dosage of 400 mg daily improved the metabolic impairment of all PCOS patients, especially in those with PCOS with familiar diabetes who have a higher grade of risk of nonalcoholic fatty liver disease (NAFLD) and predisposition to diabetes[21]. The above studies are similar to our results, and there is currently a lack of research on the combination of the two drugs, and our results further confirm that combination therapy has a significant effect on PCOS improvement. Perilous studies[6] found that the combination of alpha-lipoic acid and pioglitazone has a significant improvement effect on peripheral nerve preservation caused by diabetes.

Both alpha-lipoic acid and pioglitazone exhibited good weight and BMI control results, and this is very important in the management of PCOS. BMI is considered an indicator of insulin resistance in PCOS-affected Indian women[22]. Gunning et al[23] also discovered that preconception BMI in these PCOS women is significantly associated with BMI of their offspring at 6-8 years of age. Different PCOS phenotypes exhibit variation in BMI, with larger values in the most severe forms[24]. Using alpha-lipoic acid to treat polycystic ovarian syndrome dramatically reduced BMI[25]. However, the meta-analysis[26] found that the effectiveness of pioglitazone in lowering body mass index was considerably inferior to that of metformin. In our study, pioglitazone was found to have a significant improvement in weight and BMI.

α-Lipoic acid, which plays an essential role in mitochondrial dehydrogenase reactions, has recently gained considerable attention as an antioxidant[27]. α-Lipoic acid administration is beneficial in several oxidative stress models such as ischemia-reperfusion injury and diabetes[28]. α-Lipoic improves antioxidant balance and diminishes oxidative/glycative stress, protein nitrosative damage, inflammation, and apoptosis, mainly in the hypothalamus of insulin-resistant rats[29]. Alpha-lipoic acid shows a better effect in reversing the formation of methemoglobin, preventing DNA damage, and stimulating dapsone hydroxylamine (DDS-NOH) -induced increase in GSH[30]. Alpha-lipoic acid has hepatoprotective effects against methotrexate (MTX)-induced hepatic injury mediated by nuclear factor erythroid 2-related factor (Nrf2)/heme oxygenase-1 (HO-1) pathway as well as anti-inflammatory and antiapoptotic properties[31]. Therefore, Alpha-lipoic acid is a naturally occurring compound having antioxidant activities. It decreases cell proliferation and induces apoptotic cell death.

In women of reproductive age, PCOS is a prevalent and varied endocrine condition that is typically accompanied by metabolic abnormalities. According to tests[32] using gold-standard procedures, it was estimated that around 75% of these people have impaired insulin action. Alpha-lipoic acid caused a statistically significant decrease in AUC-I as well as an increase in overall antioxidant capacity in hyperinsulinemic individuals[20]. Insulin resistance and menstrual abnormalities are improved with pioglitazone therapy[33]. Pioglitazone is an insulin sensitizer used to treat type 2 diabetes mellitus (T2DM). It improves adipose tissue and muscle insulin resistance (IR), which is a key factor in PCOS[34].

A crucial part of the pathophysiology of PCOS is played by oxidative stress and dyslipidemia. The result is oxidative stress, which damages proteins and DNA. Normal reactive oxygen species (ROS) are involved in fetal, placental, and oocyte maturation as well as normal folliculogenesis throughout embryonic development, whereas excessive oxidative stress can cause fetal growth restriction (FGR), miscarriages, or fetal mortality[5]. The most common finding in all PCOS patients is an increase in LDL cholesterol. From the third decade of life, obese PCOS patients have lower HDL cholesterol levels, whereas triglyceride levels start to climb in the second decade of life. Obesity, hyperinsulinemia, and dyslipidemia, among other endocrine and metabolic disorders, may be to blame for the oxidative stress associated with PCOS[35]. According to research by Bannigida et al[36], women with PCOS, regardless of weight, had higher blood MDA lev-

els than the corresponding controls. According to Victor et al[37], patients with PCOS in general and those with insulin resistance, in particular, had higher rates of ROS and myeloperoxidase (MPO) levels. According to Moti et al[38], PCOS women had considerably higher levels of blood insulin and advanced oxidation protein products than women without the condition, but lower levels of total antioxidant status. Pioglitazone has been shown in animal trials[39] to reduce inflammatory biomarkers, hypertriglyceridemia, hyperglycemia, insulin resistance, and hormones linked to obesity. However, controlled-release alpha-lipoic acid administration was not linked to a rise in plasma antioxidant capacity or a fall in plasma lipid oxidation products, according to research by Masharani et al[40]. Our findings imply that while the combination of alpha-lipoic acid and pioglitazone separately does not significantly improve dyslipidemia compared to the prior study, it does considerably reduce both oxidative stress and dyslipidemia in PCOS.

Lipids are crucial elements of cells that are involved in the control of metabolism, the endocrine system, and reproductive processes. The liver and adipose tissue are the primary organs where lipid control occurs[41]. According to Wild et al[42], dyslipidemia is frequent in PCOS. Women with PCOS have greater LDL and non-HDL cholesterol independent of BMI, in addition to documented changes in triglycerides and HDL cholesterol. Metabolites of phosphatidylcholine, free fatty acids (FFAs), and polyunsaturated fatty acids (PUFAs) were abnormally present in patients with PCOS. Patients with PCOS may have conflicting impacts on their lipid profiles from circulating insulin and androgens, particularly with regard to the bioactive lipid metabolites produced from PUFAs[43]. The use of alpha-lipoic acid or pioglitazone alone is not significant for an abnormal improvement in lipid metabolism, but we discovered that the combination of the two is more evident in the improvement of lipid metabolism. This is comparable to our findings.

Limitations

There are some pitfalls in our study. The main weaknesses are the small sample size, brief duration of drug administration, and limitations to follow-up subjects for longer than three months. Therefore, additional large-scale randomized trials with longer drug use and follow-up periods are needed to evaluate the efficacy of alpha-lipoic acid and pioglitazone in PCOS-affected women.

Conclusions

We found that the combined use of insulin-sensitive drugs pioglitazone and alpha-lipoic acid has a clear effect on improving menstrual cyclicity and insulin resistance, and oxidative stress levels. However, pioglitazone alone has a better effect than alpha-lipoic acid in improving oxidative stress levels, BMI, and menstrual cyclicity.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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We would like to thank all participants and our hospital.

Ethics Approval

This study was approved by the Ethics Committee of Xuzhou First People's Hospital and the Institutional Review Board (IRB). According to the CONSORT guidelines, this study also comply with the Declaration of Helsinki. Unique protocol ID Clinical Trial Number: xznss-232123.

Informed Consent

All patients signed an informed consent form after receiving information.

Data Availability

The data used to support the findings of this study are included in the article.

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Authors' Contribution

Conception and design: YP, YYL, MS, JZ. Acquisition, analysis, and interpretation of the data: YP, YYL, MS, JZ, TTZ, BW, HH, ZLW. Drafting and writing: YP. Final approval of the article: YP, YYL, MS, JZ, TTZ, BW, HH, ZLW.

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