Effect of pioglitazone treatment on the adrenal androgen response to corticotrophin in obese patients with polycystic ovary syndrome

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BACKGROUND: To investigate the effect of pioglitazone on adrenal steroidogenesis in polycystic ovary syndrome (PCOS), we studied 11 obese (two with BMI >25 kg/m²; nine with BMI >27 kg/m²) PCOS women before and after 6 months of treatment at a dose of 45 mg/day. METHODS: During the early follicular phase, ultrasonography and hormonal assays were performed. On separate days, all women underwent an oral glucose tolerance test (OGTT), a euglycaemic hyperinsulinaemic clamp and an adrenocorticotrophin hormone (ACTH) test. The same protocol was repeated after therapy. RESULTS: Pioglitazone treatment significantly reduced the insulin response to OGTT and improved the insulin sensitivity indices (P < 0.01 and P = 0.03 respectively). A significant decrease was found in LH (P < 0.05) and androstenedione (P < 0.01) levels after therapy, whereas the other hormonal parameters improved but not significantly. Pioglitazone administration reduced the response of 17α-hydroxyprogesterone (17OHP) and androstenedione to ACTH (P < 0.01 and P < 0.02 respectively), most likely through an inhibition of cytochrome P450. The same treatment was able to rebalance the relative activity of 17,20-lyase, as documented by an increase in the androstenedione:17OHP ratio (P < 0.05) after ACTH stimulation. CONCLUSIONS: Our data support the contention that insulin enhances ACTH-stimulated steroidogenesis, while inducing a relative impairment of 17,20-lyase activity. Whether the beneficial effects of pioglitazone on this imbalance could be related to the ameliorated glyco-insulinaemic metabolism or to a direct effect on the adrenal glands remains to be determined.

Key words: adrenal glands/insulin/PCOS/pioglitazone

Introduction

Polycystic ovary syndrome (PCOS) is characterized by elevated circulating androgen levels, which seem to originate from both ovarian and adrenal glands: an excess of adrenal androgen secretion, in fact, appears to affect ~25% of patients with PCOS (Moran and Azziz, 2001), thus underlining the contribution of the adrenal component in determining the clinical disturbances typical of this syndrome.

In this regard, several lines of evidence seem to indicate a relationship between adrenal abnormalities and PCOS: for instance, this syndrome often occurs in women with congenital adrenal hyperplasia (Horrocks et al., 1982); Cushing’s syndrome and androgen-producing tumours are associated with PCOS (Kase et al., 1963); rats given excess of dehydroepiandrosterone (DHEA) develop polycystic ovaries (Roy et al., 1962). Furthermore, a hyper-responsiveness to adrenocorticotropic hormone (ACTH) has been described to varying degrees in most PCOS women (Lucky et al., 1986; Azziz et al., 1998). These findings have led several authors to propose an exaggerated and/or prolonged adrenarche as a primary aetio-pathogenic mechanism for the development of the syndrome (Lucky et al., 1986; Lazar et al., 1995).

It is widely recognized that insulin resistance and hyper-insulinaemia, which affect a large proportion of PCOS patients, may play a role in the aetiology of hyperandrogenism: at ovarian level, insulin promotes ovarian androgen secretion, playing a synergistic role with gonadotrophins both directly and stimulating insulin like-growth factor I (IGF-I) secretion (Cara and Rosenfield, 1988); in the liver it also decreases serum sex hormone-binding globulin (SHBG) synthesis (Nestler et al., 1991), thus increasing free androgen concentrations; at the adrenal level, we previously demonstrated that hyperinsulinaemia is able to potentiate in vitro ACTH-stimulated androgen production in women with PCOS (Lanzone et al., 1992); the same result was obtained by in vitro studies (Bianchi et al., 1993); more recently, it was proposed that this effect of insulin was mediated by a relative impairment of 17,20-lyase activity (Moghetti et al., 1996). In turn, modifications of insulin plasma
concentration both by the opioid antagonist naltrexone (Lanzone et al., 1994) and by metformin administration (LaMarca et al., 1999; Arslanian et al., 2002) led to a reduction in the ACTH-stimulated adrenal steroidogenesis in women affected by PCOS. Moreover, in a recent study evaluating the basal adrenal androgen levels, the thiazolidinedione pioglitazone was reported to reduce dehydroepiandrosterone sulphate (DHEAS) circulating levels (Aziz, 2003).

Pioglitazone, a new insulin-sensitizing agent belonging to the thiazolidinediones class, is able to enhance insulin action with a post-insulin receptor mechanism of action (Lehmann et al., 1995). The different chemical structure of this compound, which exhibits a higher affinity to the specific receptor peroxisome proliferator-activated receptor (PPAR)γ, allows a more potent insulin-sensitizing effect with a much lower hepatotoxicity compared with troglitazone and rosiglitazone (Gillies and Dunn, 2000). In a recent study from our group, pioglitazone administration to obese PCOS women induced an amelioration of the metabolic assessment, with a parallel improvement of several clinical and biochemical parameters typical of the syndrome (Romualdi et al., 2003). In particular, the decrease in insulin secretion obtained with pioglitazone treatment was associated with a significant reduction of basal 17α-hydroxyprogesterone (17OHP) levels in hyperinsulinemic PCOS patients, whereas the adrenal production of DHEAS remained unaffected.

On the basis of these studies, we wanted to investigate further the effect of pioglitazone on the adrenal steroidogenesis of women with PCOS, by subjecting them to ACTH stimulation before and after 6 months of pioglitazone treatment.

Materials and methods

Subjects

We recruited 11 women with PCOS (age range 18–36 years) attending our divisional outpatient services. Two of them were overweight [body mass index (BMI) >25 kg/m²], while the other nine were frankly obese (BMI >27 kg/m²). All the women had spontaneous onset of puberty and normal sexual development, and all had oligomenorrhea with chronic anovulation since post-menarcheal age. All the women were euthyroid and none had taken medications known to affect plasma sex steroid levels for ≥3 months before entering the study.

PCOS was diagnosed according to the following (Homburg, 2002); the presence of clinical findings (at least two of these signs: amenorrhoea or oligomenorrhoea, hirsutism and/or acne, chronic anovulation), plasma androgen levels at the upper limit of, or above, the normal range [at least one of: free androgen index (FAI) >5; androstenedione ≥6.98 nmol/l; testosterone ≥2.0 nmol/l], and the presence of bilaterally normal or enlarged ovaries containing ≥7–10 microcysts (<5 mm in diameter) on ultrasonography, with an augmented stromal area:total area ratio (Adams et al., 1985; Fulghesu et al., 2001). A normal LH/FSH ratio was not considered an exclusion criterion. Pregnancy or possibility of pregnancy and nursing, significant liver [aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin or alkaline phosphatase ≥2 times the upper limit of normal] or renal impairment (serum creatinine >1.8 ng/ml), neoplasm, cardiovascular disease or unstable mental illness were considered exclusion criteria.

Informed consent was obtained from each patient, and the study protocol was approved by our Institutional Review Board.

Study design

Studies were conducted during the early follicular phase of spontaneous or induced [medroxyprogesterone acetate (MPA) 10 mg/day for 7 days] menstrual cycles (day 3–7).

After following a standard carbohydrate diet (300 g/day) for 3 days and fasting overnight for 10–12 h, blood samples were collected in order to perform the following laboratory assays: basal hormone assessment, hepatic and renal chemistries. On the same day, patients underwent an oral glucose tolerance test (OGTT). The OGTT was performed as follows: at 09:00 after overnight fasting, an indwelling catheter was inserted into the antecubital vein of one arm. Blood samples were collected basally and after ingestion of 75 g glucose in 150 ml water, within 5 min, and at 30, 60, 90, 120, 180 and 240 min. Insulin, glucose and C-peptide were assayed in all samples.

On the following day, after a 10 h overnight fast, a hyperinsulinemic–euglycaemic clamp was performed to estimate peripheral insulin sensitivity. At 08:00, an i.v. catheter was placed in the antecubital vein for the infusion of glucose and insulin. Another catheter was placed in the dorsal vein of the contralateral hand for blood withdrawal and warmed to 65°C with a warming box. A constant infusion of insulin (Actrapid HM; Novo Nordisk, Denmark) 40 mU/m² per min was started (De Fronzo et al., 1979). After reaching the steady-state velocity for the insulin infusion within 10 min in order to achieve steady-state insulin levels of ~717 pmol/l during the clamp (range 574–897 pmol/l), a variable infusion of 20% glucose was begun via a separate infusion pump and the rate was adjusted, on the basis of plasma glucose samples drawn every 5 min, to maintain plasma glucose between 4.4 and 4.99 mmol/l. The plasma glucose level was determined by the glucose oxidase technique with a glucose analyser (Beckman Instruments, USA). The plasma infusion rate during the last 60 min of a 2 h infusion was then taken as the estimate of peripheral insulin sensitivity and measured as ‘M’ (mg/kg/min).

On the last day of hospitalization, after overnight bed rest and fasting, an ACTH test was performed as follows: at 07:00 an indwelling catheter was inserted into the antecubital vein and saline solution was infused slowly throughout the test in order to keep the vein patent. Blood samples were collected just before and 60 min after the injection of 250 μg of ACTH (Synacthen; Ciba–Geigy, Italy). Plasma cortisol DHEAS, androstenedione, testosterone and 17OHP were assayed.

The first day of the following menstruation, therapy with pioglitazone was started: one pill of 45 mg daily in the morning for 6 months. During the study, chronically stabilized therapies not interfering with the parameters under evaluation were permitted. The use of antidiabetic and/or estroprogestinic drugs was not allowed. Patients were recommended not to modify their usual diet.

The main parameters of liver function were monitored each month during the treatment.

Following pioglitazone treatment, all patients had a second hospitalization at menstrual days 3–7 and repeated the same protocol study.

Assays

Plasma samples for glucose concentration were collected in tubes containing an inhibitor of glycolysis (sodium fluoride) and were analysed within 5 h. Plasma glucose concentrations were determined by the glucose oxidase technique with a glucose analyser (Beckman, USA). Plasma samples for insulin and C-peptide concentrations were placed in tubes standing in ice, centrifuged for 10 min at 1000 g using a 4226 ALC Centrifuge (ALC, Italy) and remained frozen at −30°C until assayed.
considered statistically significant. For all analyses, 
and any significant difference was identified by using the Bonferroni correction for multiple comparisons. 

The ratio of testosterone\(\times100\):(SHBG) was used to calculate the FAI.

The response to ACTH was evaluated on the basis of plasma hormone levels detected 60 min after the injection. The apparent activities of 17,20-lyase and 17\(\alpha\)-hydroxylase were calculated with the product/precursor ratios (androstenedione 17OHP and 17OHP progesterone respectively), as previously described (La Marca et al., 1983).

All data are presented as mean ± SD. The signficance of differences among the pre- and post-treatment measures was determined with the use of one-way analysis of variance and any significant difference was identified by using the Bonferroni correction for multiple comparisons. For all analyses, 

Table I shows the clinical and endocrine features of the 11 PCOS patients included in the study before and after pioglitazone treatment. At baseline, all had normal fasting glycaemic values. Only one subject showed an impaired glucose tolerance. The treatment was well-tolerated and no alterations were detected in either renal or hepatic chemistries. BMI was not modified after pioglitazone treatment. Plasma values of FSH, estradiol, progesterone and prolactin were not affected by drug treatment. A significant decrease in LH circulating concentrations was found in our study group after pioglitazone therapy (4.56 ± 2.96 versus 6.95 ± 3.78 mIU/ml (mean ± SD); 

Table I. Clinical and hormonal data of polycystic ovary syndrome women before and after 6 months of pioglitazone treatment

<table>
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<tr>
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<th>Pre-treatment</th>
<th>Post-treatment</th>
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<tr>
<td>Body mass index (kg/m(^2))</td>
<td>31.96 ± 4.15</td>
<td>31.90 ± 3.78</td>
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<tr>
<td>FSH (IU/ml)</td>
<td>4.90 ± 1.47</td>
<td>4.75 ± 1.27</td>
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<tr>
<td>LH (IU/ml)</td>
<td>6.95 ± 3.78</td>
<td>4.56 ± 2.96*</td>
</tr>
<tr>
<td>Estradiol (pmol/l)</td>
<td>159.86 ± 73.48</td>
<td>179.88 ± 120.56</td>
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<tr>
<td>Progesterone (nmol/l)</td>
<td>2.54 ± 0.70</td>
<td>2.75 ± 1.59</td>
</tr>
<tr>
<td>Prolactin (μg/l)</td>
<td>22.13 ± 6.06</td>
<td>18.04 ± 8.89</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>24.67 ± 11.67</td>
<td>29.57 ± 9.53</td>
</tr>
<tr>
<td>FAI (testosterone/100:SHBG)</td>
<td>10.79 ± 5.73</td>
<td>7.69 ± 3.74</td>
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Values are presented as means ± SD. *P < 0.05.
FAI = free androgen index; SHBG = sex hormone-binding globulin.

Results

Table I shows the clinical and endocrine features of the 11 PCOS patients included in the study before and after pioglitazone treatment. At baseline, all had normal fasting glycaemic values. Only one subject showed an impaired glucose tolerance.

The treatment was well-tolerated and no alterations were detected in either renal or hepatic chemistries. BMI was not modified after pioglitazone treatment. Plasma values of FSH, estradiol, progesterone and prolactin were not affected by drug treatment. A significant decrease in LH circulating concentrations was found in our study group after pioglitazone therapy (4.56 ± 2.96 versus 6.95 ± 3.78 mIU/ml (mean ± SD); 

The response to ACTH was evaluated on the basis of plasma hormone levels detected 60 min after the injection. The apparent activities of 17,20-lyase and 17\(\alpha\)-hydroxylase were calculated with the product/precursor ratios (androstenedione 17OHP and 17OHP progesterone respectively), as previously described (La Marca et al., 1983).

All data are presented as mean ± SD. The signficance of differences among the pre- and post-treatment measures was determined with the use of one-way analysis of variance and any significant difference was identified by using the Bonferroni correction for multiple comparisons. For all analyses, 

Table II shows basal plasma concentrations of cortisol, androstenedione, 17OHP, DHEAS and testosterone, and the plasma values of the same hormones 60 min after ACTH injection, all before and after pioglitazone treatment. Intravenous administration of ACTH significantly enhanced all plasma steroid concentrations (P = 0.014 for testosterone, 
P < 0.01 for androstenedione, 17OHP and cortisol), except DHEAS. The presence of a late-onset adrenal enzymatic defect was excluded in all patients on the basis of baseline and ACTH-stimulated 17OHP values, according to published criteria (New et al., 1983).

Pioglitazone treatment was effective in reducing basal androstenedione plasma concentrations (6.14 ± 2.48 versus 4.32 ± 1.81 nmol/l; P < 0.01). The basal mean values of all the other adrenal steroids decreased after 6 months of therapy, although not always significantly. The administration of pioglitazone was associated with a significant reduction in 17OHP and androstenedione in response to ACTH injection (P < 0.01 and P < 0.02 respectively versus baseline).
Table II. Basal and adrenocorticotrophic hormone (ACTH)-stimulated steroid secretion in polycystic ovary syndrome patients before and after 6 months of pioglitazone treatment

<table>
<thead>
<tr>
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<th>Pre-treatment</th>
<th>Post-treatment</th>
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<tr>
<td>Cortisol (nmol/l)</td>
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<tr>
<td>Basal</td>
<td>4.32 ± 4.08</td>
<td>6.05 ± 4.57</td>
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<tr>
<td>60 min after ACTH</td>
<td>13.80 ± 1.57</td>
<td>20.25 ± 2.27</td>
</tr>
<tr>
<td>DHEAS (nmol/l)</td>
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<tr>
<td>Basal</td>
<td>2.73 ± 2.20</td>
<td>4.23 ± 2.84</td>
</tr>
<tr>
<td>60 min after ACTH</td>
<td>8.21 ± 6.48</td>
<td>12.30 ± 8.68</td>
</tr>
<tr>
<td>17OHP (nmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>298.79 ± 36.12</td>
<td>376.48 ± 46.23</td>
</tr>
<tr>
<td>60 min after ACTH</td>
<td>650.37 ± 74.23</td>
<td>638.08 ± 93.73</td>
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Values are expressed as mean ± SD.

Figure 3. Basal ratio of 17OHP to progesterone (P), which indicates 17α-hydroxylase activity, and basal and ACTH-stimulated ratios of androstenedione to 17OHP, which indicates 17,20-lyase activity before (black bars) and after (empty bars) pioglitazone treatment.

No significant changes occurred in the basal ratio of 17OHP progesterone, which indicates 17α-hydroxylase activity, and in the basal ratio of androstenedione 17OHP, which indicates 17,20-lyase activity, after 6 months of pioglitazone treatment (1.63 ± 0.78 versus 1.32 ± 0.51 and 1.53 ± 0.76 versus 1.25 ± 0.56 respectively; P > 0.05). Nevertheless, analysing the same parameters after ACTH stimulation, we observed a significant variation in the apparent enzymatic activity of 17,20-lyase (androstenedione 17OHP ratio), which rose from the baseline mean value of 0.90 ± 0.41 to 1.11 ± 0.42 at the end of the therapy (P < 0.05) (Figure 3).

Discussion

Despite the high number of published papers, the link between PCOS and adrenal abnormalities is not yet clearly defined. Some patients with PCOS have clinical and endocrine features resembling a congenital adrenal hyperplasia or cryptic enzymatic defect (Meikle et al., 1984; Benjamin et al., 1996). Similarly, a continuation of exaggerated adrenarche suggests a chronic adrenal hyperfunction in these women (Lucky et al., 1986). Furthermore, most authors agree on the presence of an adrenal androgen hyper-responsiveness to ACTH in at least a proportion of the PCOS population (Lanzone et al., 1992; Gonzalez, 1997; Azziz et al., 1998).

However, circulating levels as well as diurnal rhythms of ACTH are generally similar in normal and PCOS subjects (Horrocks et al., 1983). These findings suggest that the increased adrenal androgen production in patients with PCOS derives from an altered adrenal responsiveness or from an abnormal adrenal stimulation by factors other than ACTH.

In this context, insulin is believed to constitute a candidate for the stimulation of the adrenal cortex. We have previously reported an increase in serum 17OHP and androstenedione responses to ACTH in hyperinsulinaemic PCOS subjects in respect of PCOS women with normal insulin levels and controls (Lanzone et al., 1992). This contention was indirectly supported by the evidence that a normalization of insulin secretion, obtained with a long-term treatment with the opioid antagonist naltrexone, was able to decrease the adrenal 17OHP and androstenedione response to ACTH in PCOS hyperinsulinaemic patients (Lanzone et al., 1994). In the present study, 6 months therapy with pioglitazone at a dose of 45 mg/day was effective in decreasing the insulinaemic response to OGTT and, in line with previous reports in the literature, in ameliorating the steroid milieu of our patients. The same treatment was able to significantly decrease the adrenal secretion of 17OHP in response to an ACTH bolus and to reduce the production of androstenedione under the same experimental conditions. No differences in ACTH-stimulated DHEAS levels seem to emerge from the comparison between pre- and post-treatment values.

Cytochrome P450-17α (cP450-17α) is a key enzyme required for the synthesis of all androgens and is expressed in both ovarian and adrenal cells (Miller et al., 1988; Fevold et al., 1989). It catalyses the conversion of pregnenolone to DHEA and, at least in the rat, of progesterone to androstenedione through two sequential steps: 17 hydroxylation and 17,20-lyase. Hence, an abnormal regulation of the cP450-17α activity, perhaps through the insulin/IGF system (Rosenfield et al., 1990), may represent the common pathway leading to the hyperactive steroidogenesis in the adrenals and gonads of many PCOS women.

The acute in vivo effects of insulin on the activities of 17,20-lyase and 17α-hydroxylase, calculated with the precursor/product ratios, was elegantly evaluated by Moghetti et al. Experimentally induced hyperinsulinaemia, within the high physiological range, was able to shift the ACTH-stimulated adrenal steroidogenesis toward the production of the 17α-hydroxycorticosterone intermediates 17OHP and 17OHP-pregnolone. This effect was likely due to a stimulation of the cP450c17α leading to an increase of the 17α-hydroxylase and 17,20-lyase activity, with the former being enhanced markedly more than the latter (Moghetti et al., 1996). In the present study, the 17α-hydroxylase activity was calculated only before...
ACTH stimulation, as progesterone was not assayed during the test. However, in line with the previous hypotheses, the 17OHP progesterone basal ratio was slightly, though not significantly, lower after pioglitazone treatment and such decrease was entirely due to a reduction of 17OHP plasma levels. Concerning the 17,20-lyase activity, the basal androstenedione 17OHP ratio remained the same before and after pioglitazone treatment; interestingly, when this was calculated from the ACTH-stimulated steroid levels, pioglitazone treatment led to an overall decrease in the response of both the steroids, but with a more consistent reduction of the 17-ketosteroid intermediate 17OHP, thus resulting in slight relative increase in the apparent 17,20-lyase activity. These data are in line with the above-mentioned previous studies and support the hypothesis that insulin might represent the ‘trigger’ factor responsible not only for the abnormal hyperstimulation of the adrenal cP450c17 (Ehrmann et al., 1992), but also for its dysregulation (relative impairment of 17,20-lyase activity) typical of PCOS.

Whether this mechanism might constitute an intrinsic characteristic of all the patients affected by the syndrome or whether it might explain only in part the pathophysiology of the PCOS-related hyperandrogenism, remains controversial.

Few studies exist on the impact of insulin-lowering drugs on the adrenal steroid biosynthesis in patients with PCOS. La Marca et al. (1999) reported a generalized significant reduction in the response of all adrenal steroids to corticotrophin as well as in the activity of 17α-hydroxylase and 17,20-lyase after a single month of metformin treatment in unselected PCOS subjects. In contrast, we failed to observe any modification in testosterone and DHEAS response to ACTH injection in our pioglitazone-treated patients. This discrepancy is not easily explained. In fact, the authors did not provide any data regarding the change in the metabolic assessment of the subjects studied, thus the correlation between the decrease in insulin levels and the reduction in the adrenal steroidogenesis remains unclear. It could be hypothesized that the different chemical structure and pharmacological properties of pioglitazone in respect of metformin could influence in a different and, perhaps, more selective manner the steroidogenic pathway. Nevertheless, Arlt et al. recently studied the effect of different classes of insulin-lowering drugs on the ‘humanized yeast’ that express the P450c17 gene. They demonstrated that insulin might represent the ‘trigger’ factor responsible not only for the abnormal hyperstimulation of the adrenal cP450c17 (Ehrmann et al., 1992), but also for its dysregulation (relative impairment of 17,20-lyase activity) typical of PCOS.

The only report in the literature on the in vivo effect of thiazolidinediones on the adrenal steroidogenesis in PCOS patients is represented by a study from Azziz et al. (2003), who demonstrated a significant reduction in basal DHEAS levels after 20 weeks of treatment with troglitazone.

In conclusion, the present study is the first trial testing the effect of pioglitazone on the adrenal response to ACTH in obese adult PCOS patients with a complete assessment of the hormonal and metabolic changes that occurred during the treatment. Our findings point towards an overactivity and a dysregulation of the adrenal P450c17, which seems to be attenuated by the pharmacological reduction of insulin levels; however, a direct inhibitory effect of pioglitazone on this enzyme cannot be excluded.

Beside the intrinsic complexity of the endocrine–metabolic nature of PCOS, most of the disagreement on the relationship between insulin and adrenal function probably originates from the lack of standardized inclusion criteria, study designs, duration and interventions. Further studies are needed to enhance our understanding in this field.

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