RESEARCH LETTER

Adrenal hyperandrogenism and parameters of glucose metabolism in polycystic ovary syndrome

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Introduction Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among women of reproductive age. Its main clinical characteristics include oligomenorrhea or amenorrhea and symptoms of hyperandrogenism, such as hirsutism and acne. Previous data show that insulin plays an important role in the pathogenesis of PCOS, participating in ovarian and adrenal steroidogenesis regulation, as well as decreasing the level of sex hormone–binding globulin (SHBG), which in consequence increases the levels of free androgens.[1,2]

While the sources of elevated androgen levels in women with PCOS are both ovaries and adrenal glands, only in 5% of the PCOS cases, hyperandrogenism is caused by isolated adrenal steroidogenesis.[3] 17-Hydroxyprogesterone (17-OHP) acts as an intermediate in the process of steroidogenesis, being converted to 11-deoxycortisol in a cortisol-forming pathway, or androstenedione in the sex-hormone pathway.[3] Dehydroepiandrosterone (DHEA) is known as a precursor of androstenedione. Alternatively, it can be converted into dehydroepiandrosterone sulfate (DHEA-S) by DHEA-sulfotransferase. Since the presence of this enzyme was not detected in the ovary, DHEA-S seems to be the marker of adrenal androgen production.[3] Thus, the adrenal source of androgens can be verified by the confirmation of an increase in DHEA-S, as well as 17-OHP levels in the adrenocorticotropic hormone (ACTH) stimulation test.[4]

Recently, several studies have reported a relationship between insulin resistance and concentration of adrenal androgens, mostly in acute hyperinsulinemia, usually during hyperinsulinemic euglycemic clamp. The aim of our study was to assess the levels of 17-OHP and DHEA-S in relation to the indices of insulin resistance and insulin sensitivity based on the easily available standard oral glucose tolerance test (OGTT) in women with PCOS.

Patients and methods The study population consisted of 54 women, including 35 with PCOS and 19 healthy individuals as the control group. The diagnosis of PCOS was established based on the Rotterdam criteria.[5] The study protocol was approved by the Ethics Committee of the Medical University of Bialystok (APK.002.176.2021), and followed the principles of the Declaration of Helsinki. All the participants were informed about the study protocol and signed the written consent.

All the women underwent anthropometric measurements and were screened for clinical signs of hyperandrogenism including the assessment of acne. They also self-assessed their body hair presence according to the modified Ferriman–Gallwey score, where a score of 8 and above is indicative of hirsutism.[6] The ovarian morphology was assessed on transvaginal ultrasonography up to the 10th day of the menstrual cycle or independently of the cycle phase in the cases of amenorrhea. Blood samples were taken in the follicular phase, between the 3rd and 7th day of the menstrual cycle or independently of the cycle phase in the cases of amenorrhea. Hormone levels were measured for luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (TT), SHBG, and DHEA-S. All the participants underwent the OGTT with the assessment of glucose and insulin concentrations at the baseline, as well as after 60 and 120 minutes. Based on glucose and insulin concentrations during OGTT,

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the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and the Matsuda index were calculated.[7] Additionally, the ACTH-stimulation test assessing 17-OHP concentrations at baseline (17-OHP 0 min), after 60 minutes (17-OHP 60 min), and the difference between them (Δ17-OHP) was performed for all the participants.

Serum glucose concentrations were assessed with the hexokinase method. Serum insulin, LH, FSH, and SHBG levels were evaluated by the immunoradiometric method (DIAsource ImmunoAssays S.A., Louvain-la-Nueve, Belgium). TT, DHEA-S, and 17-OHP levels were determined by radioimmunoassay (DIAsource ImmunoAssays S.A.). During the ACTH-stimulation test, the patients were given 250 μg of synthetic ACTH (Synacthen 0.25 mg/ml, Alfasgima, Warsaw, Poland).

Statistical analysis Normality of the variable distribution was tested with the Shapiro–Wilk test. Due to the non-normal distribution of the data, the differences between the 2 compared groups were evaluated with the Mann–Whitney test and the correlation between the variables was assessed with the Spearman test. A *P* value below 0.05 was considered significant. The data analyses were performed using the Statistica package (Statistica 13.3, Statsoft, Kraków, Poland).

Results The patients from the PCOS and control group did not differ in their body mass index (median, 23.46 kg/m^2; interquartile range [IQR], 21.19–28.41) and age (median, 25 years; IQR, 22–28), both $P > 0.05$. The PCOS group was distinguished by higher free androgen index (FAI) and TT, 17-OHP at 0 minutes, and DHEA-S concentrations, as well as lower SHBG level. Polycystic ovarian morphology, manifested in increased ovarian volume and follicle count, was characteristic of the women with PCOS.

The PCOS group had higher glucose concentrations at 60 and 120 minute in the OGTT, as well as insulin concentration at 120 minute in the OGTT than the control group. Detailed characteristics of the groups are presented in Supplementary material, *Table S1*.

The PCOS group showed a positive correlation between the concentrations of TT and insulin at 60 minute in the OGTT (R = 0.5; $P = 0.04$), a positive correlation between FAI and insulin at 0 minutes, and HOMA-IR (R = 0.76; $P = 0.001$; and R = 0.67; $P = 0.005$, respectively). Furthermore, we found a negative correlation between Δ17-OHP and the Matsuda index (R = –0.77; $P = 0.002$) in the PCOS group. We did not observe any significant correlations between the parameters of glucose metabolism and DHEA-S, 17-OHP 0 min, or 17-OHP 60 min (all $P > 0.05$). All analyzed correlations in the PCOS group are presented in **TABLE 1**.

Discussion Among the factors stimulating adrenal steroidogenesis in PCOS, insulin resistance with coexistent hyperinsulinemia remain the most significant ones, and are considered crucial for PCOS pathogenesis.[8] Whether abnormalities in glucose homeostasis and insulin concentration contribute to increased androgen production in PCOS is not well established.

The higher concentrations of glucose at 60 and 120 minute, as well as of insulin at 120 minute in the OGTT noted for the PCOS group in comparison with the healthy individuals indicated that the women with PCOS were distinguished by chronic hyperinsulinemia. While HOMA-IR reflects only fasting glucose and insulin concentrations, the Matsuda index involves not only fasting but also postprandial glucose and insulin levels. Additionally, alterations in and hypersecretion of adrenal androgens in the PCOS group clearly demonstrate a response to ACTH stimulation. In our study, we concluded that Δ17-OHP correlated negatively with the Matsuda index in the PCOS patients, which might suggest the influence of hyperinsulinemia on 17-OHP hyperresponsiveness. This is in agreement with another study[9] that compared androgen production in response to ACTH stimulation in a group of hyperandrogenic women during saline infusion and acute hyperinsulinemia evoked by insulin infusion during hyperinsulinemic euglycemic clamp. In other studies,[10,11] where the relationship between insulin sensitivity and steroidogenesis in PCOS was assessed with the frequently sampled intravenous glucose tolerance test, no correlation was found between insulin sensitivity and the change in androgen concentrations,[10] or the androgen response in the ACTH-stimulation test,[11] which was contrary to our findings.

In a study by Lanzone et al,[12] the women with PCOS were stratified into normo- and hyperinsulinemic groups based on the OGTT results. That work indicated that the basal levels of 17-OHP and DHEA-S were increased and comparable in both subgroups. This may suggest that 17-OHP and DHEA-S concentrations are regulated not only by insulin. This hypothesis could explain the lack of correlations between 17-OHP 0 min and DHEA-S concentrations and parameters of glucose metabolism in our study. However, in the same work by Lanzone et al,[12] the authors found significantly higher Δ17-OHP levels after ACTH stimulation in hyperinsulinemic women with PCOS, as compared with the normoinsulinemic patients with PCOS, as well as healthy individuals, suggesting that chronic hyperinsulinemia favors the response to ACTH.

The links between DHEA-S and the parameters of chronic or acute hyperinsulinemia vary broadly between different studies. While a negative correlation between the basal concentration of DHEA-S and HOMA-IR[13] or fasting insulin levels in PCOS patients[14] was reported, the research conducted by Hines et al[15] suggests an increased activity of sulfotransferase in hyperinsulinemia, resulting in the increase of DHEA-S levels.

TABLE 1 Relationships of serum concentration of androgens and Δ17-hydroxyprogesterone with the parameters of glucose metabolism in the polycystic ovary syndrome group

Parameter	Glucose 0 min OGTT	Glucose 60 min OGTT	Glucose 120 min OGTT	Insulin 0 min OGTT	Insulin 60 min OGTT	Insulin 120 min OGTT	HOMA-IR	Matsuda index
TT, ng/ml	R = –0.3 *P* = 0.1	R = 0.15 *P* = 0.43	R = 0.23 *P* = 0.21	R = 0.33 *P* = 0.18	R = 0.5 *P* = 0.04[a]	R = 0.39 *P* = 0.12	R = 0.15 *P* = 0.55	R = –0.23 *P* = 0.37
DHEA-S, µg/dl	R = –0.12 *P* = 0.67	R = –0.24 *P* = 0.37	R = –0.29 *P* = 0.28	R = 0.24 *P* = 0.38	R = –0.08 *P* = 0.76	R = 0.3 *P* = 0.25	R = 0.16 *P* = 0.55	R = 0.02 *P* = 0.94
FAI	R = 0.08 *P* = 0.73	R = –0.14 *P* = 0.56	R = –0.04 *P* = 0.85	R = 0.76 *P* = 0.001[a]	R = 0.3 *P* = 0.27	R = –0.08 *P* = 0.76	R = 0.67 *P* = 0.005[a]	R = –0.37 *P* = 0.16
17-OHP 0 min, ng/ml	R = 0.21 *P* = 0.26	R = 0.03 *P* = 0.88	R = –0.12 *P* = 0.54	R = 0.05 *P* = 0.84	R = –0.4 *P* = 0.11	R = –0.16 *P* = 0.55	R = 0.1 *P* = 0.68	R = 0.11 *P* = 0.68
17-OHP 60 min, ng/ml	R = 0.38 *P* = 0.05	R = 0.27 *P* = 0.2	R = 0.11 *P* = 0.58	R = 0.3 *P* = 0.3	R = –0.2 *P* = 0.5	R = –0.06 *P* = 0.84	R = 0.49 *P* = 0.08	R = –0.43 *P* = 0.15
Δ17-OHP, ng/ml	R = 0.22 *P* = 0.27	R = 0.35 *P* = 0.09	R = 0.26 *P* = 0.21	R = 0.23 *P* = 0.42	R = 0.4 *P* = 0.17	R = 0.3 *P* = 0.31	R = 0.36 *P* = 0.2	R = –0.77 *P* = 0.002[a]

Data are derived from the Spearman correlation coefficient.

a The level of significance was set at $P < 0.05$

SI conversion factors: to convert DHEA-S to µmol/l, multiply by 0.027; 17-OHP to nmol/l by 2.118.

Abbreviations: DHEA-S, dehydroepiandrosterone sulfate; FAI, free androgen index; HOMA-IR, homeostasis model assessment of insulin resistance; OGTT, oral glucose tolerance test; 17-OHP, 17-hydroxyprogesterone; TT, total testosterone

The main limitation of our study is a small number of participants in the studied groups.

Conclusions In conclusion, our findings confirm increased levels of adrenal androgens in PCOS. The OGTT with insulin assessed at various time points gives us a full picture of carbohydrate disorders in PCOS. The ACTH-stimulation test shows hyperresponsiveness of adrenal glands in PCOS. The association of indices of insulin sensitivity with 17-OHP response to ACTH reflects the possible insulin impact on adrenal androgen excess, which strongly enhances the recommendations of a low glycemic index diet, as well as insulin-sensitizing drugs in PCOS treatment. Taking into account other mechanisms regulating the process of androgen production in PCOS, this subject requires further studies in larger groups of patients.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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