Clinical Significance of Adiponectin in Patients with Polycystic Ovary Syndrome Under Different Free Testosterone Index and Insulin Resistance Levels: Postprint

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Abstract

Background: Polycystic ovary syndrome is closely associated with insulin resistance and free testosterone index, yet substantial research remains necessary to provide references for its diagnosis and treatment.

Objective: To investigate the clinical significance of adiponectin in patients with polycystic ovary syndrome under varying free testosterone index and insulin resistance levels.

Methods: A total of 161 subjects, including healthy women of reproductive age and PCOS patients, were randomly selected from outpatients and inpatients at the Affiliated Hospital of Zunyi Medical University (enrolled between October 2017 and May 2020). All PCOS patients were divided into PCOS with hyperandrogenemia group and PCOS without hyperandrogenemia group based on the presence of concurrent hyperandrogenemia. Furthermore, the association between adiponectin and free testosterone index in PCOS patients across different serum testosterone levels was analyzed using the quartile method.

Results: The adiponectin level in PCOS patients with hyperandrogenemia was significantly lower than that in PCOS patients without hyperandrogenemia [(126.18$±26.21)$mg/dl$vs.(174.96±18.15)$mg/dl, $P < 0.001]. $The degree of insulin resistance was significantly more severe than that in PCOS patients without hyperan$ $IR value 5.19±3.24 vs. 3.77±$1.89, P<0.001). Under different testosterone concentration groupings, adiponectin was negatively correlated with free testosterone index and HOMA-IR regardless of whether patients had concurrent hyperandrogenemia or obesity (P<0.01 or <0.001). Multiple stepwise regression analysis results showed that regardless of whether PCOS patients

had concurrent HA, free testosterone index and HOMA-IR were the main influencing factors of serum adiponectin level (P<0.01 or <0.001), and adiponectin was the main influencing factor of FAI (P<0.01 or <0.001).

Conclusion: Under different testosterone concentrations, adiponectin levels in PCOS patients are closely related to free testosterone index and insulin resistance and are mutually main influencing factors. Measuring serum adiponectin level can simultaneously reflect the free testosterone index and insulin resistance degree in PCOS patients. Adiponectin may serve as an indicator for simultaneously evaluating hyperandrogenemia and insulin resistance in patients with polycystic ovary syndrome.

Full Text

Clinical Significance of Adiponectin in Polycystic Ovary Syndrome Patients Under Different Free Testosterone Index and Insulin Resistance Levels

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Abstract

Background: Polycystic ovary syndrome (PCOS) is closely associated with insulin resistance and free testosterone index, yet extensive research remains needed to provide reference for its diagnosis and treatment.

Objective: To investigate the clinical significance of adiponectin in PCOS patients under different free testosterone index (FAI) and insulin resistance levels.

Methods: A total of 161 healthy women of childbearing age and PCOS patients were randomly selected from outpatients and inpatients at the Affiliated Hospital of Zunyi Medical University between October 2017 and May 2020. All PCOS patients were divided into PCOS with hyperandrogenemia and PCOS without hyperandrogenemia groups. The correlation between adiponectin and free testosterone index in PCOS patients under different serum testosterone levels was further analyzed using quartile analysis.

Results: Adiponectin levels in PCOS patients with hyperandrogenemia were significantly lower than in those without hyperandrogenemia [(126.18$±26.21)$mg/dl vs (174.96±18.15)$mg/dl, $P < 0.001$]. The degree of insulin resistance was also significant IR 5.19±3.24 vs 3.77±$1.89, P<0.001). Across different testosterone concentration subgroups, adiponectin was negatively correlated with both free testosterone index and HOMA-IR regardless of hyperandrogenemia or obesity status (P<0.01 or P<0.001). Multivariate stepwise regression analysis showed that regardless of hyperandrogenemia status, free testosterone index and HOMA-IR were the main influencing factors of serum adiponectin levels (P<0.01 or P<0.001), and adiponectin was the main influencing factor of FAI (P<0.01 or P<0.001).

Conclusion: In PCOS patients under different testosterone concentrations, adiponectin levels are closely related to both free testosterone index and insulin resistance, with these factors mutually influencing each other. Serum adiponectin measurement can simultaneously reflect both free testosterone index and insulin resistance degree in PCOS patients, suggesting that adiponectin may serve as an indicator for evaluating both hyperandrogenemia and insulin resistance in PCOS.

Keywords: Polycystic ovary syndrome; Adiponectin; Testosterone; Free testosterone index; Insulin resistance

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Introduction

Polycystic ovary syndrome (PCOS) is a clinical syndrome characterized primarily by hyperandrogenemia, anovulation (such as oligomenorrhea, amenorrhea, infertility), and polycystic ovarian morphology [1]. Previous studies have demonstrated a close relationship between hyperandrogenism and insulin levels in patients, where elevated blood insulin promotes increased androgen synthesis, affecting normal follicular development and leading to hirsutism, menstrual disorders, and even infertility [2,3]. Additionally, increased androgen levels affect insulin sensitivity in various target cells from multiple perspectives, exacerbating insulin resistance to some extent and significantly increasing patients' risks of hypertension, hyperlipidemia, cardiovascular disease, and type 2 diabetes compared to normal individuals [4].

Adiponectin (ADPN) is a protein hormone with physiological roles in energy

metabolism, anti-inflammation, promotion of follicular development and ovulation, and pregnancy [5]. As a cytokine primarily secreted by adipocytes, it significantly influences serum sex hormone and insulin concentrations in PCOS patients [6]. Animal experiments have shown that adiponectin can reduce androgen production by affecting luteinizing hormone receptor gene expression in theca cells [5]. Meanwhile, in PCOS patients, serum adiponectin levels are negatively correlated with insulin resistance, and measuring serum adiponectin can clinically predict the degree of insulin resistance [7].

This study preliminarily investigated the correlation between FAI and adiponectin in PCOS patients under different serum testosterone concentrations, aiming to explore whether adiponectin could serve as an indicator for simultaneously evaluating both hyperandrogenemia and insulin resistance in PCOS.

Methods

1.1 General Data According to the Rotterdam diagnostic criteria proposed by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) in 2003 [7], we selected 116 PCOS patients (divided into hyperandrogenemia and non-hyperandrogenemia groups) and 45 healthy normal controls as study subjects, all from outpatients and inpatients at the Affiliated Hospital of Zunyi Medical University between October 2017 and April 2020. This study was approved by the hospital ethics committee, and all subjects signed informed consent forms.

Exclusion criteria:
1. Other diseases that could cause increased androgen levels or changes in adiponectin (including but not limited to endocrine diseases such as congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing' s syndrome);
2. Pregnant women;
3. Women who had taken steroid hormones within 6 months.

All subjects underwent detailed inquiry regarding menstrual history, reproductive history, family history, past medical history, and medication history. Manifestations of androgen excess such as hirsutism and acne were observed. Height, weight, BMI, waist circumference, and hip circumference were measured. All patients denied history of assisted reproduction, smoking, or drug use.

On days 3-5 of the menstrual cycle or when no dominant follicle was observed on ultrasound in patients with irregular menstruation, fasting elbow venous blood was collected after 12 hours of fasting by dedicated personnel to detect the following biochemical indicators: glycated hemoglobin, fasting plasma glucose, plasma insulin concentration, blood lipids (cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein), follicle-stimulating hormone, luteinizing hormone, progesterone, testosterone, sex hormone-binding globulin, and dehydroepiandrosterone sulfate. Serum adiponectin levels were measured by enzyme-linked immunosorbent assay. Body mass index (BMI = weight/height^2),

free androgen index (FAI = total testosterone/sex hormone-binding globulin × 100), waist-to-hip ratio (WHR = waist circumference/hip circumference), and homeostasis model assessment of insulin resistance [HOMA-IR = fasting glucose (mmol/L) × fasting insulin (U/ml)/22.5] were calculated.

1.2 Methods According to previous guidelines, hyperandrogenemia was defined as serum testosterone concentration ≥ 2.44 ng/ml [7]. All 116 PCOS patients were divided into two groups based on hyperandrogenemia status: PCOS with hyperandrogenemia group (HA group, n=65) and PCOS without hyperandrogenemia group (non-HA group, n=51).

Further, based on quartile values of serum testosterone concentration, both HA and non-HA groups were divided into four subgroups:
- HA group: Quartile 1 (<2.62 mg/dL, n=15), Quartile 2 (2.62-2.77 mg/dL, n=16), Quartile 3 (2.77-3.16 mg/dL, n=17), Quartile 4 (>3.16 mg/dL, n=17)
- Non-HA group: Quartile 1 (<1.01 mg/dL, n=14), Quartile 2 (1.01-1.23 mg/dL, n=11), Quartile 3 (1.23-1.65 mg/dL, n=16), Quartile 4 (>1.65 mg/dL, n=10)

The mean age of all patients was (24.38$±5.03)$years, and mean BMI was (24.53±3.90)kg/m^{2}. Forty-five healthy and average age 26.18$±$3.65 years, with regular menstrual cycles of 28-32 days.

To further understand differences in general biochemical indicators and sex hormones among PCOS patients with different BMI levels, all subjects with BMI < 24 kg/m^2 were divided into PCOS normal weight group (PCOS+NW, n=47) and non-PCOS normal weight group (non-PCOS+NW, n=21). Subjects with BMI ≥ 24 kg/m^2 were divided into PCOS overweight group (PCOS+OW, n=69) and non-PCOS overweight group (non-PCOS+OW, n=24).

1.3 Statistical Analysis Data were processed using SPSS 22.0 software. All data were analyzed after fully controlling for confounding factors and balancing baseline data. Quantitative data with normal distribution were expressed as x±s, while non-normally distributed data were expressed as M(Q1,Q3). Independent samples t-test was used for inter-group comparisons when data met normal distribution; otherwise, non-parametric tests were used. Pearson correlation analysis was used to understand correlations between indicators. Stepwise multiple linear regression analysis was used to determine relationships between independent and dependent variables. P<0.05 was considered statistically significant.

Results

2.1.1 Comparison of General Data and Clinical Biochemical Indicators Compared with the normal control group, the HA and non-HA PCOS groups showed significantly increased weight, BMI, waist circumference, hip circumference, WHR, FPG, FINS, HOMA-IR, HbA1c, TG, and LDL-C, while HDL-C was significantly decreased (P<0.05). Comparison between HA and non-HA

groups revealed that HOMA-IR and TG levels were significantly higher in the HA group, while HDL-C was significantly lower (P<0.05). See .

2.1.2 Comparison of Sex Hormones and Adiponectin Levels The HA group showed significantly higher FSH, testosterone, and FAI compared with the normal control group, while progesterone, SHBG, and adiponectin were lower (P<0.05). The non-HA group also showed increased FSH, testosterone, and FAI compared with controls (P<0.05). Between HA and non-HA groups, FSH, progesterone, SHBG, and adiponectin gradually decreased, while testosterone and FAI increased (P<0.05). See .

2.1.3 PCOS Patients Grouped by Testosterone Quartiles Further analysis after grouping all PCOS patients by serum testosterone quartiles revealed that adiponectin levels gradually decreased with increasing quartile groups in the HA group. This phenomenon persisted in quartiles 1, 3, and 4 of the non-HA group and was statistically significant (P<0.05). Within-group analysis showed that adiponectin levels in each quartile group were significantly lower than in the corresponding non-HA group (P<0.05). See .

2.2 Comparison of PCOS Patients and Control Group by BMI One-way ANOVA showed that PCOS patients had significantly lower progesterone, adiponectin, and HDL-C compared with control subjects at the same BMI level, while FINS, FPG, HOMA-IR, testosterone, and FAI were significantly higher (P<0.01). PCOS+OW group showed significantly lower adiponectin levels and higher serum testosterone and free testosterone index compared with PCOS+NW group (P<0.01). See .

2.3.1 Correlation Analysis Results After BMI Adjustment After BMI adjustment in all PCOS patients, adiponectin was negatively correlated with HOMA-IR (r=-0.485, P<0.001), FAI (r=-0.607, P<0.001), and testosterone (r=-0.725, P<0.001). In the HA group, adiponectin was negatively correlated with FAI (r=-0.405, P=0.006), testosterone (r=-0.542, P<0.001), and HOMA-IR (r=-0.352, P=0.018). In the non-HA group, adiponectin was negatively correlated with FAI (r=-0.583, P=0.006) and HOMA-IR (r=-0.469, P=0.032), but not significantly correlated with testosterone (r=-0.416, P=0.061).

2.3.1 Regression Analysis Results with FAI and Adiponectin as Dependent Variables After BMI Adjustment After BMI adjustment, multiple linear regression analysis using height, weight, HOMA-IR, blood lipids, and sex hormones as independent variables and FAI and adiponectin as dependent variables (Y) was performed using the stepwise method (entry criteria α=0.05, removal criteria α=0.1).

In the non-HA group:
- With FAI as dependent variable (Y), the regression equation was Y=-0.066X1-

0.135X2+19.034 (r^2=0.539), where X1 was adiponectin and X2 was BMI, indicating that adiponectin and BMI were important influencing factors of FAI after controlling for other variables.
- With adiponectin as dependent variable (Y), the regression equation was Y=-6.744X1-7.91X2-1.748X3+250.486 (r^2=0.688), where X1 was HOMA-IR, X2 was FAI, and X3 was BMI, indicating that HOMA-IR, FAI, and BMI were important influencing factors of adiponectin. Collinearity analysis showed VIF values <5, suggesting no significant collinearity. See .

In the HA group:
- With FAI as dependent variable (Y), the regression equation was Y=-0.123X1+36.407 (r^2=0.207), where X1 was adiponectin, indicating that adiponectin was an important influencing factor of FAI.
- With adiponectin as dependent variable (Y), the regression equation was Y=-1.266X1-2.663X2+262.429 (r^2=0.273), where X1 was FAI and X2 was HOMA-IR, indicating that FAI and HOMA-IR were important influencing factors of adiponectin. Collinearity analysis showed VIF values <5, suggesting no significant collinearity. See .

Discussion

Polycystic ovary syndrome is the leading cause of reproductive dysfunction in 40% of women of childbearing age [8]. Women with PCOS often have systemic metabolic disturbances, such as hyperinsulinemia and resulting diabetes, coronary heart disease, hypertension, and hyperlipidemia [9]. Due to the complex and uncertain pathogenesis of PCOS, there are currently no definitive diagnostic indicators in clinical practice, with diagnosis primarily based on comprehensive clinical manifestations.

Adiponectin, as a biologically active protein hormone, plays multiple roles including anti-atherosclerosis, participation in lipid metabolism, steroid hormone synthesis, and improvement of insulin resistance [10]. Recent studies have found it to be closely related to PCOS diagnosis [11]. Previous research suggests that obesity is likely one of the main clinical manifestations of PCOS patients [12]. Surveys show that 40%-80% of women with PCOS have varying degrees of overweight, and PCOS symptoms improve significantly in most patients after weight reduction [8]. Additionally, larger adipocyte volume is associated with lower adiponectin levels and more pronounced relative waist circumference increase [13]. Studies have shown that PCOS patients have significantly lower ovarian expression of adiponectin receptors compared with normal patients [14]. Increasing adiponectin levels can improve metabolic function in PCOS experimental mice exposed to androgen-induced dihydrotestosterone and increase progesterone and estradiol synthesis induced by FSH and insulin-like growth factor 1 (IGF-1) in the ovary. Testosterone can upregulate inflammatory signaling pathways in adipose tissue, reduce inflammatory cytokines such as IL-6 and TNF-α, and affect adiponectin secretion [6]. Furthermore, hyperandrogen levels have different regulatory effects on preadipocyte proliferation and differ-

entiation. Studies on androgen receptor knockout mice suggest that androgens may affect preadipocyte proliferation and differentiation [15].

Our study found that regardless of hyperandrogenemia or obesity status, higher androgen levels in PCOS patients were associated with lower adiponectin and more severe insulin resistance. This result is consistent with existing related research and further confirms the special relationship between insulin resistance and androgens in the pathophysiological development of PCOS [16]. Combined with Singh et al.' s research, the mechanisms may include: (1) Decreased adiponectin can induce insulin resistance, relatively increase insulin levels, and enhance the action of P450c17a in the ovary and kidney, leading to increased androgen or its precursors. (2) Excessive testosterone inhibits insulin binding to target cells and relatively increases insulin levels, which exacerbates insulin resistance in PCOS patients, further leading to decreased adiponectin [17,18].

Therefore, considering the close relationship among obesity, androgens, and adiponectin, we first grouped all patients by BMI index to understand whether adiponectin and androgen levels differed in non-obese PCOS patients compared with obese PCOS patients and normal controls. The results showed that regardless of obesity status, PCOS patients had significantly higher BMI, serum testosterone concentration, fasting glucose, and insulin resistance levels compared with normal controls, while adiponectin levels were significantly lower. We then grouped patients by hyperandrogenemia status and found that the phenomenon of decreasing adiponectin levels with increasing testosterone levels also occurred in the non-HA group, suggesting that BMI and testosterone have combined effects on adiponectin secretion, consistent with previous research by Singh et al. [17].

Correlation analysis after BMI adjustment showed that regardless of hyperandrogenemia status, adiponectin levels decreased with increasing FAI values as testosterone concentrations rose. This further suggests that testosterone may affect adiponectin secretion through insulin resistance target organs other than adipose tissue. Targeted increase of adiponectin levels may improve hyperandrogenemia symptoms and insulin resistance in PCOS patients, thereby ameliorating the development of PCOS.

Currently, clinical diagnosis of PCOS with hyperandrogenemia relying solely on serum testosterone concentration, while simple, has a high missed diagnosis rate due to the complex phenotypes of PCOS patients. Diagnosis combining clinical manifestations, although more accurate, is highly subjective and heavily dependent on clinicians' experience and judgment. FAI is the most objective clinical indicator for evaluating androgen excess. Patients with higher FAI values have been confirmed to be more prone to ovarian hyperstimulation syndrome (OHSS). Due to differences in insulin resistance, metabolism, and hyperandrogenic phenotype, FAI values vary across different PCOS phenotypes, making FAI a potential diagnostic indicator for PCOS with hyperandrogenemia [18,19]. Previous studies have shown that PCOS patients have significantly lower adiponectin levels than normal individuals, which can serve as a predictor for PCOS disease pro-

gression [20]. We verified the relationship among adiponectin, FAI, and insulin resistance at different testosterone concentration levels through multiple regression analysis. The BMI-adjusted multiple regression analysis results indicated that adiponectin is the main influencing factor of FAI, and FAI and HOMA-IR are also main influencing factors of adiponectin, which is basically consistent with the above research. Meanwhile, this study found no mutual influence between FAI and adiponectin with age, progesterone, LH, or FSH, suggesting that adiponectin can serve as a relatively stable indicator for disease prediction.

In summary, considering the interplay among FAI, adiponectin, and insulin resistance, adiponectin, as an important adipokine affecting insulin, androgen, and lipid metabolism levels in PCOS patients, can reflect both hyperandrogen levels and insulin resistance degree in PCOS patients through serum adiponectin measurement, independent of testosterone concentration. Therefore, measurement of serum adiponectin levels is expected to become an important reference indicator for PCOS diagnosis and condition assessment.

Conflict of Interest: All authors declare no conflict of interest.

References

[1] Eiras M, Pinheiro D, Romcy K, et al. Polycystic Ovary Syndrome: the Epigenetics Behind the Disease. Reprod Sci, 2022, 29(3): 680-694. DOI: 10.1007/s43032-021-00516-3.
[2] Zehravi M, Maqbool M, Ara I. Polycystic ovary syndrome and infertility: an update. I J Adolesc Med Health, 2021. DOI: 10.1515/ijamh-2021-0073.
[3] Wang J, Wu D, Guo H, et al. Hyperandrogenemia and insulin resistance: The chief culprit of polycystic ovary syndrome. Life Sci, 2019, 236: 116940. DOI: 10.1016/j.lfs.2019.116940.
[4] Yang R, Yang S, Li R, et al. Effects of hyperandrogenism on metabolic abnormalities in patients with polycystic ovary syndrome: a meta-analysis. Reprod Biol Endocrinol, 2016, 14(1): 67. DOI: 10.1186/s12958-016-0203-8.
[5] Esmaili S, Hemmati M, Karamian M. Physiological role of adiponectin in different tissues: a review. Arch Physiol Biochem, 2020, 126(1): 67-73. DOI: 10.1080/13813455.2018.1493606.
[6] He Y, Lu L, Wei X, et al. The multimerization and secretion of adiponectin are regulated by TNF-alpha. Endocrine, 2016, 51(3): 456-468. DOI: 10.1007/s12020-015-0741-4.
[7] Chang S, Dunaif A. Diagnosis of Polycystic Ovary Syndrome: Which Criteria to Use and When? Endocrinol Metab Clin North Am, 2021, 50(1): 11-23. DOI: 10.1016/j.ecl.2020.10.002.
[8] Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol, 2018, 14(5): 270-284. DOI: 10.1038/nrendo.2018.24.
[9] Khan MJ, Ullah A, Basit S. Genetic Basis of Polycystic Ovary Syndrome (PCOS): Current Perspectives. Appl Clin Genet, 2019, 12: 249-260. DOI: 10.2147/TACG.S200341.

[10] Fang H, Judd RL. Adiponectin Regulation and Function. Compr Physiol, 2018, 8(3): 1031-1063. DOI: 10.1002/cphy.c170046.
[11] Baldani D, Skrgatic L, Kasum M, et al. Altered leptin, adiponectin, resistin and ghrelin secretion may represent an intrinsic polycystic ovary syndrome abnormality. Gynecol Endocrinol, 2019, 35(5): 401-405. DOI: 10.1080/09
[12] Shirazi FKH, Khodamoradi Z, Jeddi M. Insulin resistance and high molecular weight adiponectin in obese and non-obese patients with Polycystic Ovarian Syndrome (PCOS). BMC Endocr Disord, 2021, 21(1): 45. DOI: 10.1186/s12902-021-00710-z.
[13] Benrick A, Chanclón B, Micallef P, et al. Adiponectin protects against development of metabolic disturbances in a PCOS mouse model. Proc Natl Acad Sci USA, 2017, 114(34): 7187-7196. DOI: 10.1073/pnas.1708854114.
[14] Bongrani A, Mellouk N, Rame C, et al. Ovarian Expression of Adipokines in Polycystic Ovary Syndrome: A Role for Chemerin, Omentin, and Apelin in Follicular Growth Arrest and Ovulatory Dysfunction? Int J Mol Sci, 2019, 20(15): 3778. DOI: 10.3390/ijms20153778.
[15] Benrick A, Chanclón B, Micallef P, et al. Adiponectin protects against development of metabolic disturbances in a PCOS mouse model. Proc Natl Acad Sci USA, 2017, 114(34): 7187-7196. DOI: 10.1073/pnas.1708854114.
[16] Moghetti P, Tosi F. Insulin resistance and PCOS: chicken or egg? J Endocrinol Invest, 2021, 44(2): 233-244. DOI: 10.1007/s40618-020-01351-0.
[17] Singh A, Bora P, Krishna A. Direct action of adiponectin ameliorates increased androgen synthesis and reduces insulin receptor expression in the polycystic ovary. Biochem Biophys Res Commun, 2017, 488(3): 509-515. DOI: 10.1016/j.bbrc.2017.05.076.
[18] Nikbakht R, Zargar M, Moramezi F, et al. Insulin Resistance and Free Androgen as Predictors for Ovarian Hyperstimulation Syndrome in Non-PCOS Women. Horm Metab Res, 2020, 52(2): 104-108. DOI: 10.1055/a-1079-534
[19] Ożga K, Krzyczkowska-Sendrakowska M, Hubalewska-Dydejczyk A, et al. The value of the free androgen index depends on the phenotype of polycystic ovary syndrome - a single-centre experience. Endokrynol Pol, 2019, 70(4): 330-335. DOI: 10.5603/EP.a2019.0017.
[20] Gupta V, Mishra S, Mishra S, et al. L:A ratio, Insulin resistance and metabolic risk in women with polycystic ovarian syndrome. Diabetes Metab Syndr, 2017, S697-S701. DOI: 10.1016/j.dsx.2017.05.001.

Note: Figure translations are in progress. See original paper for figures.