Correlation Analysis Between Different Free Testosterone Index Levels and Clinical Characteristics in Patients with Polycystic Ovary Syndrome: Postprint

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Abstract

Background Polycystic ovary syndrome (PCOS) is a common reproductive and metabolic disorder, with hyperandrogenemia being a major clinical characteristic in POCS patients. The free androgen index (FAI) is not only significant in diagnosing hyperandrogenemia, but is also closely associated with clinical indicators such as glucose and lipid metabolism in PCOS patients. Objective To investigate the correlation between different FAI levels and clinical characteristics of PCOS patients. Methods A retrospective analysis was conducted on 468 PCOS patients who visited the Gynecology Clinic of the First Affiliated Hospital of Heilongjiang University of Chinese Medicine between October 2019 and June 2021. According to tertiles of FAI levels, patients were divided into low FAI level (LFAI) group (FAI$ $2.57, n=156) and medium FAI level (MFAL) group (2.576.70, n=156); data on general conditions, sex hormone levels, glucose and lipid metabolism levels, thyroid hormone levels, and uric acid levels were collected for the three groups; Pearson correlation analysis was used to explore the correlation between FAI levels and clinical indicators in the three groups. Results In the HFAI group, FAI was positively correlated with body mass (r=0.301), BMI (r=0.318), waist circumference (r=0.362), hip circumference (r=0.307), waist-to-hip ratio (WHR) (r=0.280), testosterone (T) (r=0.581), androstenedione (AND) (r=0.407), 60-minute glucose (r=0.298), 120-minute glucose (r=0.279), 180-minute glucose (r=0.281), fasting insulin (FINS) (r=0.415), 60-minute insulin (r=0.320), 120-minute insulin (r=0.362), 180-minute insulin (r=0.447), homeostasis model assessment of insulin resistance (HOMA-IR) (r=0.446), and uric acid (r=0.265) (P<0.05), and negatively correlated with SHBG (r=-0.486) (P<0.05). Conclusion FAI levels are closely associated with glucose and lipid metabolism indicators in PCOS patients, and screening for and attention to clinical indicators such as glucose and

lipid metabolism should be enhanced for PCOS patients with high FAI levels.

Full Text

Correlation Analysis between Different Free Testosterone Index Levels and Clinical Characteristics of Patients with Polycystic Ovary Syndrome

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a common reproductive and metabolic disorder primarily characterized by hyperandrogenemia. The free testosterone index (FAI) is not only important in diagnosing hyperandrogenemia but is also closely associated with clinical parameters such as glucose and lipid metabolism indexes in PCOS patients.

Objective: To investigate the association between different FAI levels and the clinical characteristics of PCOS patients.

Methods: A total of 468 PCOS patients who attended the gynecology outpatient clinic of the First Affiliated Hospital of Heilongjiang University of Chinese Medicine between October 2019 and June 2021 were retrospectively analyzed. Based on FAI tertiles, patients were divided into three groups: low FAI level (LFAI) group (FAI $\leq$ 2.57, n=156), medium FAI level (MFAI) group (2.57 $<$ FAI $\leq$ 6.70, n=156), and high FAI level (HFAI) group (FAI $>$ 6.70, n=156). General information, sex hormone levels, glucose and lipid metabolism parameters, thyroid hormone levels, and uric acid levels were collected for all three groups. Pearson correlation analysis was used to examine the relationship between FAI levels and clinical parameters.

Results: In the HFAI group, FAI was positively correlated with body weight (r=0.301), BMI (r=0.318), waist circumference (r=0.362), hip circumference (r=0.307), waist-hip ratio (WHR) (r=0.280), testosterone (T) (r=0.581), androstenedione (AND) (r=0.407), 60-minute glucose (r=0.298), 120-minute glucose (r=0.279), 180-minute glucose (r=0.281), fasting insulin (FINS) (r=0.415), 60-minute insulin (r=0.320), 120-minute insulin (r=0.362), 180-minute insulin (r=0.447), homeostatic model assessment of insulin resistance (HOMA-IR) (r=0.446), and uric acid (r=0.265) (P$<$0.05), while it was

negatively correlated with sex hormone-binding globulin (SHBG) (r=-0.486) (P<0.05).

Conclusion: FAI levels are closely related to glucose and lipid metabolism indexes in PCOS patients. Enhanced screening and monitoring of metabolic parameters are crucial for PCOS patients with high FAI levels.

Keywords: Polycystic ovary syndrome; Testosterone; Androgens; Ovarian cysts; Thyroid hormones; Uric acid

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age, with a prevalence of 8%-13% [1]. Chronic hyperandrogenism is a key pathogenic mechanism in PCOS [2]. Diagnostic criteria for PCOS vary, but hyperandrogenemia (HA) represents one of the most critical diagnostic indicators. Elevated androgen levels, including free testosterone (FT), total testosterone (TT), free androgen index (FAI), dehydroepiandrosterone sulfate (DHEAS), and androstenedione (AND), can be used to assess HA at the biochemical level [3]. FAI is not only closely associated with the incidence of metabolic syndrome but also represents an important factor affecting fertility outcomes in infertile PCOS patients [4].

Currently, research establishing FAI cutoff values for diagnosing PCOS is limited in China, and few studies have examined the correlation between different FAI levels and clinical characteristics in PCOS patients. As an effective indicator for evaluating HA, the relationship between FAI and clinical features of PCOS warrants further investigation [5]. Therefore, this study conducted a retrospective analysis of PCOS patients to explore the clinical characteristics and influencing factors across different FAI levels, aiming to provide valuable insights for clinical diagnosis and treatment.

Methods

Study Design and Participants This retrospective analysis included 468 PCOS patients diagnosed at the gynecology outpatient clinic of the First Affiliated Hospital of Heilongjiang University of Chinese Medicine between October 2019 and June 2021. Based on FAI levels, patients were divided into tertiles: low FAI level (LFAI) group (FAI $\leq$ 2.57, n=156), medium FAI level (MFAI) group (2.57 $<$ FAI $\leq$ 6.70, n=156), and high FAI level (HFAI) group (FAI $>$ 6.70, n=156). The study was approved by the Ethics Committee of the First Affiliated Hospital of Heilongjiang University of Chinese Medicine (approval number: HZYLKY201800601).

Diagnostic Criteria PCOS diagnosis followed the "Chinese Guidelines for the Diagnosis and Treatment of Polycystic Ovary Syndrome" [6]: (1) Oligomenorrhea, amenorrhea, or irregular uterine bleeding as essential criteria; (2) Fulfillment of at least one of the following: HA and/or clinical manifestations of hyperandrogenism; Polycystic ovary morphology on ultrasound; (3) Exclusion of other androgen-excess disorders.

Data Collection **General Information:** Age, blood pressure, height, body weight, BMI, waist circumference, hip circumference, and waist-hip ratio (WHR) were collected.

Sex Hormone Indicators: Blood samples were collected on days 3-5 of the menstrual cycle or after progesterone-induced withdrawal bleeding, between 3-5 days after bleeding onset. Serum samples were obtained after overnight fasting and measured using radioimmunoassay. Parameters included follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), DHEAS, androstenedione (AND), sex hormone-binding globulin (SHBG), and FAI [calculated as FAI = T (g/L) / SHBG (nmol/L) × 100], as well as the LH/FSH ratio.

Glucose and Lipid Metabolism Parameters: Fasting blood glucose (FBG), 30-minute glucose, 60-minute glucose, 120-minute glucose, 180-minute glucose, fasting insulin (FINS), 30-minute insulin, 60-minute insulin, 120-minute insulin, 180-minute insulin, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A (APOA), apolipoprotein B (APOB), lipoprotein a (LPa), and HOMA-IR [calculated as HOMA-IR = FBG (mmol/L) × FINS (U/mL) / 22.5].

Thyroid Hormone and Uric Acid Levels: Free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), thyroglobulin antibodies (TGAb), and uric acid.

Statistical Analysis Statistical analysis was performed using SPSS 26.0 software. Normally distributed continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm s$). Inter-group comparisons were conducted using one-way ANOVA, with pairwise comparisons performed using LSD-t tests. Pearson correlation analysis was used to examine the relationship between FAI levels and other clinical parameters. $P<0.05$ was considered statistically significant.

Results

Comparison of General Characteristics and Sex Hormone Levels Among Three Groups There were no significant differences in age, diastolic blood pressure, height, or hip circumference among the three groups ($P>0.05$). However, significant differences were observed in systolic blood pressure, body

weight, BMI, waist circumference, WHR, FSH, LH, LH/FSH ratio, T, DHEAS, AND, and SHBG (P<0.05). Specifically, the HFAI group showed higher body weight, BMI, waist circumference, WHR, DHEAS, and AND compared to both the LFAI and MFAI groups (P<0.05). The HFAI group also had higher systolic blood pressure and T levels but lower LH and LH/FSH ratio compared to the MFAI group, along with lower SHBG levels (P<0.05). Both the MFAI and HFAI groups had lower FSH levels than the LFAI group (P<0.05), while the MFAI group had a higher LH/FSH ratio than the LFAI group (P<0.05) .

Comparison of Glucose and Lipid Metabolism Levels Among Three Groups Significant differences were found among the three groups in 30-minute glucose, 60-minute glucose, 120-minute glucose, FINS, 30-minute insulin, 60-minute insulin, 120-minute insulin, 180-minute insulin, HOMA-IR, TG, HDL-C, APOB, and uric acid levels (P<0.05). The HFAI group exhibited higher levels of 60-minute glucose, 120-minute glucose, FINS, 30-minute insulin, 60-minute insulin, 180-minute insulin, HOMA-IR, TG, APOB, and uric acid compared to both the LFAI and MFAI groups (P<0.05). Additionally, the HFAI group showed higher 120-minute insulin and lower HDL-C levels compared to the LFAI group, and higher 30-minute glucose levels compared to the MFAI group (P<0.05) .

Correlation Analysis Correlation Between FAI Levels and General Characteristics/Sex Hormones: In the LFAI group, FAI was negatively correlated with age and SHBG (P<0.05) and positively correlated with T (P<0.05). In the MFAI group, FAI was negatively correlated with body weight, BMI, waist circumference, hip circumference, and WHR (P<0.05) and positively correlated with T (P<0.05). In the HFAI group, FAI was positively correlated with body weight, BMI, waist circumference, hip circumference, WHR, T, and AND (P<0.05) and negatively correlated with SHBG (P<0.05) .

Correlation Between Different FAI Levels and Glucose/Lipid Metabolism and Thyroid Hormones: In the LFAI group, FAI was positively correlated with APOA (P<0.05) and negatively correlated with 30-minute glucose and uric acid (P<0.05). In the MFAI group, FAI was positively correlated with 60-minute insulin, TG, APOB, and uric acid (P<0.05). In the HFAI group, FAI was positively correlated with 60-minute glucose, 120-minute glucose, 180-minute glucose, FINS, 60-minute insulin, 120-minute insulin, 180-minute insulin, HOMA-IR, and uric acid (P<0.05) .

Discussion

Hyperandrogenism is a hallmark feature of PCOS. In addition to insulin resistance, elevated HA can lead to metabolic disturbances. Studies have found that HA in PCOS patients reduces the sensitivity of hypothalamic gonadotropin-releasing hormone neurons to estrogen and progesterone, resulting in signifi-

cantly increased gonadotropin-releasing hormone and LH secretion, while relative FSH deficiency leads to abnormal follicular development and reduced conversion of AND and DHEAS to estrogen [11]. Increased LH inhibits hepatic SHBG production, thereby increasing free testosterone levels [11]. Our results showed that both MFAI and HFAI groups had lower FSH levels than the LFAI group, while the HFAI group had lower LH levels than the MFAI group, consistent with these findings.

Testosterone can increase serum uric acid levels by inducing hepatic purine nucleotide metabolism or upregulating expression of the urate reabsorption transporter system Smct1 [12]. Studies have shown that SHBG is negatively correlated with uric acid levels in premenopausal obese women, and the potential mechanism of reduced SHBG levels may be related to AMPK inactivation in hepatocytes caused by elevated uric acid concentrations [13]. Our study found that the HFAI group had higher uric acid levels than both the LFAI and MFAI groups, and FAI was positively correlated with uric acid levels in both the medium and high FAI groups. Research has demonstrated that testosterone levels are positively correlated with serum uric acid levels and the prevalence of hyperuricemia in women with PCOS [14], consistent with our findings.

The HFAI group in our study also showed higher TSH levels than the MFAI group. Thyroid function is closely related to the hypothalamic-pituitary-ovarian axis, and thyroid dysfunction can affect sex hormone secretion. Cai et al. [15] found that PCOS patients with TSH $\geq$ 2.5 mU/L had significantly elevated FAI levels and reduced SHBG levels. Subclinical hypothyroidism is associated with increased body weight, increased SHBG, and enhanced conversion of androstenedione to testosterone [16], and elevated androgen levels can worsen insulin resistance, which is also linked to increased TSH [17].

Obesity and insulin resistance are common complications in women with PCOS, and obesity can exacerbate insulin resistance, HA, and metabolic syndrome [8]. Our study found that the HFAI group had higher levels of 30-minute and 60-minute glucose, 30-minute, 60-minute, and 180-minute insulin, FINS, HOMA-IR, TG, and APOB compared to the LFAI and MFAI groups. Correlation analysis revealed that in the HFAI group, FAI was positively correlated with 60-minute, 120-minute, and 180-minute glucose, FINS, 60-minute, 120-minute, and 180-minute insulin, and HOMA-IR. HOMA-IR stimulates ovarian androgen synthesis and reduces testosterone levels, thereby inhibiting hepatic SHBG production and increasing androgen bioactivity, leading to HA [9]. Elevated androgen levels increase lipolysis and free fatty acids, affecting glucose uptake and utilization and resulting in insulin resistance [10].

Our study also found that the HFAI group had higher body weight, BMI, waist circumference, and WHR than the LFAI and MFAI groups, with higher systolic blood pressure than the MFAI group. Correlation analysis showed that in both the MFAI and HFAI groups, FAI was positively correlated with BMI, waist circumference, hip circumference, and WHR. Research indicates that obese patients have more severe HA [7]. The positive rates of diagnosing HA using AND

and FAI are higher than using T alone, and elevated FAI levels can effectively evaluate HA [7]. Our study demonstrates that FAI levels are closely associated with glucose and lipid metabolism parameters, thyroid dysfunction, and other metabolic disturbances in PCOS patients, with high FAI levels showing more severe metabolic and hormonal imbalances.

Conclusion

FAI levels are closely related to glucose and lipid metabolism indexes in PCOS patients. High FAI levels are associated with more severe metabolic and hormonal disturbances. Therefore, PCOS patients with elevated FAI levels should receive enhanced screening and monitoring of metabolic parameters to enable early prevention of complications. This study had certain geographical limitations in patient recruitment; future multi-center studies are needed to reduce the impact of single-center sampling and improve diagnostic accuracy for PCOS and its complications.

References

[1] KHAN M J, ULLAH A, BASIT S. Genetic basis of polycystic ovary syndrome (PCOS): current perspectives[J]. Appl Clin Genet, 2019, 12: 249-260. DOI: 10.2147/tacg.s200341.

[2] ESCOBAR-MORREALE H F. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment[J]. Nat Rev Endocrinol, 2018, 14(5): 270-284. DOI: 10.1038/nrendo.2018.24.

[3] DE MEDEIROS S F, BARBOSA B B, DE MEDEIROS A K L W Y, et al. Differential effects of various androgens on polycystic ovary syndrome[J]. Horm Metab, 2021, 53(5): 341-349. DOI: 10.1055/a-1422-3243.

[4] ZHANG D J, GAO J S, LIU X K, et al. Effect of three androgen indexes (FAI, FT, and TT) on clinical, biochemical, and fertility outcomes in women with polycystic ovary syndrome[J]. Reprod Sci, 2021, 28(3): 775-784. DOI: 10.1007/s43032-020-00345-2.

[5] ZHANG B J, WANG J, SHEN S M, et al. Association of androgen excess with glucose intolerance in women with polycystic ovary syndrome[J]. Biomed Res Int, 2018, 2018: 6869705. DOI: 10.1155/2018/6869705.

[6] Endocrinology Group and Guidelines Expert Group of the Obstetrics and Gynecology Branch of the Chinese Medical Association. Chinese Guidelines for the Diagnosis and Treatment of Polycystic Ovary Syndrome[J]. Chinese Journal of Obstetrics and Gynecology, 2018, 53(1): 2-6. DOI: 10.3760/cma.j.issn.0529-567x.2018.01.002.

[7] Wu J, Liang R, Chen Y. Significance of Different Androgen Indexes in the Diagnosis of Hyperandrogenemia in Polycystic Ovary Syndrome[J]. Zhejiang Medical Journal, 2021, 43(5): 537-539. DOI: 10.12056/j.issn.1006-2785.2021.43.5.2020-3297.

[8] BARBER T M, HANSON P, WEICKERT M O, et al. Obesity and polycystic ovary syndrome: implications for pathogenesis and novel management strategies[J]. Clin Med Insights Reprod Health, 2019, 13: 1179558119874042. DOI: 10.1177/1179558119874042.

[9] Wang DM, Li L, Hou J, et al. Correlation Between Hyperandrogenemia and Non-alcoholic Fatty Liver Disease in Patients with Polycystic Ovary Syndrome[J]. Maternal and Child Health Care of China, 2021, 36(14): 3177-3180. DOI: 10.19829/j.zgfybj.issn.1001-4411.2021.14.002.

[10] Jia CL. Effects of Obesity and Hyperandrogenemia on Metabolism in Polycystic Ovary Syndrome[D]. Nanjing: Nanjing Medical University, 2021.

[11] DING H G, ZHANG J, ZHANG F, et al. Resistance to the insulin and elevated level of androgen: a major cause of polycystic ovary syndrome[J]. Front Endocrinol (Lausanne), 2021, 12: 741764. DOI: 10.3389/fendo.2021.741764.

[12] ZHANG Y Q, CAI M L, DILIMULATI D, et al. Correlation between serum uric acid and body fat distribution in patients with polycystic ovary syndrome[J]. Front Endocrinol (Lausanne), 2021, 12: 782808. DOI: 10.3389/fendo.2021.782808.

[13] SIMÓ R, SAEZ-LOPEZ C, LECUBE A, et al. Adiponectin upregulates SHBG production: molecular mechanisms and potential implications[J]. Endocrinology, 2014, 155(8): 2820-2830. DOI: 10.1210/en.2014-1072.

[14] MU L S, PAN J X, YANG L L, et al. Association between the prevalence of hyperuricemia and reproductive hormones in polycystic ovary syndrome[J]. Reprod Biol Endocrinol, 2018, 16(1): 104. DOI: 10.1186/s12958-018-0419-x.

[15] CAI J, ZHANG Y, WANG Y Y, et al. High thyroid stimulating hormone level is associated with hyperandrogenism in euthyroid polycystic ovary syndrome (PCOS) women, independent of age, BMI, and thyroid autoimmunity: a cross-sectional analysis[J]. Front Endocrinol (Lausanne), 2019, 10: 222. DOI: 10.3389/fendo.2019.00222.

[16] ALEXANDER E K, PEARCE E N, BRENT G A, et al. 2017 guidelines of the American thyroid association for the diagnosis and management of thyroid disease during pregnancy and the postpartum[J]. Thyroid, 2017, 27(3): 315-389. DOI: 10.1089/thy.2016.0457.

[17] Li HQ, Feng YX, Chen JH, et al. Analysis of Thyroid-Stimulating Hormone and Metabolic Levels in Adolescent Females with Polycystic Ovary Syndrome[J]. Journal of Guangxi University of Chinese Medicine, 2022, 25(4): 10-12. DOI: 10.3969/j.issn.2095-4441.2022.04.004.

Author Contributions

FENG Xiaoling and YIN Wenqing conceptualized the research direction, collected and organized case data, and drafted the initial manuscript. YIN Wenqing participated in case data collection and organization. WANG Ying was responsible for manuscript revision. HOU Lihui oversaw patient management and case data provision, quality control, and final approval of the manuscript, taking overall responsibility for the article. All authors confirmed the final version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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