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Clinical study on the relationship between neopterin and polycystic ovary syndrome

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Abstract

Objectives: *Polycystic ovary syndrome (PCOS) is a reproductive endocrine and metabolic disorder. To offer new research direction for PCOS, including its pathogenesis and treatment, this research explores the relationship between neopterin (NPT) and polycystic ovary syndrome.*

Material and Methods: *This is a prospective study. 80 cases with PCOS were selected in the reproductive medicine clinics of the Second Affiliated Hospital of Shandong First Medical University as PCOS group from January 2020 to December 2021. 80 cases with normal pregnancy plan were treated as non-PCOS group, whose menstruation is from 25 days to 35 days. We divided the two groups into two subgroups separately according to their body mass index (BMI): the obese one with BMI≥25kg/m2 and non-obese one with BMI<25kg/m2.*

Results: *The expression levels of triglycerides (TG), total cholesterol (TC), fasting insulin (FINS), C-reactive protein (CRP), neutrophil (N), NPT and interleukin-6 (IL-6) in PCOS group were higher than non-PCOS group. CRP, NPT and IL-6 in the obese group were increased than the non-obese group in the pairwise comparison of its subgroups whether in PCOS group or non-PCOS group. In the analysis of linear correlation, NPT was positively correlated with TG, TC, WBC, N, CRP, FINS, IL-6 and TNF-α (P<0.01). Multivariate Stepwise regression analysis found that FINS and IL-6 was the two most important factors.*

Conclusion: *The expression of NPT in PCOS patients was higher than non-PCOS. NPT maybe play a significant role in the development of PCOS.*

Keywords: Polycystic ovary syndrome, Neopterin, IL-6, TNF-α.

Introduction

Polycystic ovary syndrome (PCOS) is a reproductive endocrine and metabolic disorder. It is clinically characterized by increased androgen level, reduced or no ovulation, irregular menstruation, and polycystic ovarian changes and often accompanied by insulin resistance and obesity [1]. Due to the complexity of PCOS etiology and the high heterogeneity of clinical manifestations, its pathogenesis remains unclear [2]. At present, there are mainly the following aspects, such as genetics, environmental factors, psychological factors and chronic inflammatory reactions [3]. Neopterin (NPT) is a kind of pterin compound with low molecular weight and a non-specific low molecular inflammatory marker. Previous studies show NPT is associated with various diseases activated by cellular immune responses, including infection, trauma, tumor, autoimmune, inflammatory response. But in present the study about NPT and PCOS is very little, and their results are inconsistent. In order to find the correlation between NPT and PCOS we performed this study. It will provide a new research direction for further research on the pathogenesis, treatment plan and prevention of long-term complications of PCOS.

Materials and Methods

Materials

This is a prospective study. All Participants were recruited from the Reproductive Medicine Clinic of the Second Affiliated Hospital of Shandong First Medical University from January 2020 to December 2021. PCOS was diagnosed according to the 2003 Rotterdam criteria with at least 2 of the following features: oligomenorrhea or amenorrhea, clinical or biochemical hyperandrogenism, and polycystic ovaries on ultrasound. Patients with oligomenorrhea or hyperandrogenism caused by any other clinical conditions were excluded, such as nonclassical congenital adrenal hyperplasia, 21-hydroxylase deficiency, Cushing's syndrome, hypothyroidism or significant elevation in serum prolactin (PRL) [4]. And at the same period, eighty infertile women with regular menstrual periods (25 days<menstrual period<35 days) were recruited as a non-PCOS group. All of them were matched with PCOS in the age, body mass index (BMI) and ethnicity.

All subjects were generally in good condition, without cardiovascular disease and diabetes, and thyroid stimulating hormone (TSH) was normal. There were no oral medications in the last six months (such as oral contraceptives, antidiabetic drugs, antihypertensive drugs, glucocorticoids, antiandrogens, ovulation-inducing drugs, diet pills or other hormonal drugs). All subjects have no bad life styles, no smoking, no alcohol, no history of mental illness, no infertility caused by congenital physiological defects, deformities or irregular menstruation, no severe allergies, no recent history of infection.

This study was approved by the Ethics Committee of Taishan Medical College (Shandong First Medical University). And all participants signed the informed consent.

Grouping

The PCOS group and the non-PCOS group were divided into two subgroups by body mass index (BMI): the obese group (BMI≥25kg/m2) and the non-obese group (BMI<25kg/m2). Among them, 36 were obese PCOS group, 44 were non-obese PCOS group, 32 were obese non-PCOS group, and 48 were non-obese non-PCOS group. The age distribution and body mass index (BMI) of the two groups met the comparison conditions (P>0.05).

Experimental Methods

All subjects were asked about their medical history by specials. For anthropometric age, height, body mass, waist circumference, hip circumference and blood pressure were recorded. Body mass index (BMI) and waist hip ratio (WHR) were calculated. Formula: BMI=weight (kg)/(height (m))2, WHR= waist circumference/hip circumference. All subjects were fasting for at least 8 hours on the morning of 3-5 days of the menstrual cycle. Serum samples were collected from elbow vein to detect neopterin, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), FINS, leukocyte (WBC), neutrophil (n) and C-reactive protein (CRP), fasting blood glucose (FPG), triglyceride (TG) and total cholesterol (TC). Fasting plasma glucose (FPG), serum triglyceride (TG) and total cholesterol (TC) were measured by automatic biochemical analyzer. The total number of white blood cells (WBC), neutrophil (N) and C-reactive protein (CRP) were measured by ABX micro CRP analyzer. FINS were detected by chemiluminescence immunization. The levels of Neopterin (NPT), interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) were determined by enzymet-linked immunosorbent assay (ELISA).

Statistical Analysis

Statistical analysis was performed using spss19.0. Descriptive characteristics are reported as mean ± standard deviation ($\bar{X}$±SD). Correlation between NPT and other indicators is analyzed by linear correlation analysis and multiple stepwise regression. The count data was analyzed by chi-square test and the measurement data was analyzed by T test. P<0.05 was considered as significant.

Result

Comparison of General Indexes between PCOS group and non-PCOS group

Age, height, weight, BMI, Waist circumference, hip circumference, WHR, systolic blood pressure, diastolic blood pressure and MAP were no significant difference between the PCOS group and the non-PCOS group (P>0.05). The results are shown in Table 1.

According to the vaginal B-ultrasound examination, the total number of follicles in the PCOS group was significantly more than that of the non-PCOS group, and the difference was statistically significant (P<0.01). The results were shown in Table 1.

Table 1: General indicators of the PCOS group and the non-PCOS group ($\bar{x} \pm s$).

	PCOS group (n=80)	non-PCOS group (n=80)
Age	28.95±5.27	27.55±4.87
Height (cm)	162.52±4.61	162.34±5.83
Weight (kg)	62.17±9.06	56.52±7.31
BMI (kg/m2)	22.83±3.22	22.09±2.73
Waist circumference (cm)	81.65±7.13	75.31±6.29
Hip circumference (cm)	93.83±6.50	91.78±6.05
WHR	0.78±0.03	0.73±0.08
Systolic pressure (mmHg)	121.85±8.16	117.91±10.58
Diastolic blood pressure (mmHg)	78.54±8.01	76.32±8.09
MAP (mmHg)	92.01±7.68	90.52±6.89
Left ovarian Fc number (number)	19.52±6.51	7.85±2.54*
Right ovarian Fc number (number)	20.84±6.78	7.79±5.21*
Total number of follicles	38.65±11.85	15.02±5.67*
*Compared with experimental group p<0.05		

Comparison of Biochemical and Inflammatory Markers between PCOS Group and Non-PCOS Group

The PCOS group had higher level of TG, TC, FINS, N and CRP than the non-PCOS group (P<0.05). Compared with the non-obese PCOS group, TG and FINS of the obese PCOS group were increased (P<0.05). However no difference was found between the two subgroups of no-PCOS in terms of TG and FINS. While the comparison of the subgroups showed that the CRP of the obese people whether in the PCOS group or in the non-PCOS group were all significantly higher than those in the non-obese group (P<0.05). There was no significant difference of FBG between the PCOS group and the non-PCOS group (P>0.05). The results were shown in Table 2 and Table 3.

Table 2: Comparison of biochemical and inflammatory markers between the two groups ($\bar{x} \pm s$).

	PCOS group (n=80)	non-PCOS group (n=80)
FPG (mmol/L)	5.18±0.27	4.85±0.81
FINS (mIU/L)	19.27±15.79	10.97±4.22*
TG (mmol/L)	1.63±0.67	0.77±0.31*
TC (mmol/L)	4.91±0.27	4.35±0.54*
WBC (*109/L)	5.83±1.52	5.66±1.61
N (*109/L)	3.50±1.25	1.50±0.34*
CRP (mg/dl)	7.83±1.30	2.24±0.70*
*Compared with PCOS group p<0.05		

Table 3: Comparison of the biochemical and inflammatory markers in each subgroup.

	PCOS group		non-PCOS group	
	Obese n=36	Non-obese n=44	Obese n=32	Non-obese n=48
FPG (mmol/L)	5.28±0.56	5.12±0.45	4.92±0.82	4.81±0.93
FINS (mIU/L)	26.80±19.57	11.73±4.17*	11.36±4.60	9.80±2.92
TG (mmol/L)	1.85±0.35	1.24±0.62*	0.85±0.04	0.67±0.15
TC (mmol/L)	5.12±0.92	4.73±0.87	4.35±0.68	4.17±0.71
WBC (*109/L)	5.62±1.42	6.52±1.56	5.58±1.48	6.15±1.58
N (*109/L)	3.30±1.36	3.86±1.27	1.42±1.32	1.83±1.27
CRP (mg/dl)	11.84±1.24	4.24±0.32*	4.36±0.58	1.84±0.13#
*Compared with PCOS obese group p<0.05; #Compared with non-PCOS obese group p<0.05				

Comparison of NPT,IL-6 *And* TNF-α *Between* PCOS *Group and Non-*PCOS *Group*

NPT and IL-6 were significantly different between the PCOS group and the non-PCOS group, while there was no significant difference of TNF-α between the two group. Compared with the subgroups, the levels of NPT and IL-6 in the obese PCOS group and the obese non-PCOS group were significant higher than those in the non-obese patients. The results were shown in Table 4 and Table 5.

Table 4: The NPT, IL-6, TNF-α of the two groups ($\bar{x} \pm s$).

	PCOS group (n=80)	non-PCOS group (n=80)
NPT (ng/ml)	16.86±2.57	6.87±2.49*
IL-6 (ug/ml)	342.03±42.52	157.63±18.59*
TNF-α (ug/L)	0.61±0.12	0.48±0.07
*Compared with PCOS group p<0.05		

Table 5: Comparison of the levels of NPT, IL-6, and TNF-α in each subgroup.

	PCOS group		non-PCOS group	
	Obese n=36	Non-obese n=44	Obese n=32	Non-obese n=48
NPT(ng/ml)	21.53±3.54	10.78±2.23*	9.45±2.51	4.58±1.35#
IL-6 (ug/ml)	446.67±58.59	232.68±21.32*	185.36±12.78	129.37±13.42#
TNF-α(ug/L)	0.62±0.12	0.58±0.14	0.51±0.08	0.46±0.08
*Compared with PCOS obese group p<0.05 ; #Compared with non-PCOS obese group p<0.05				

Linear Correlation Analysis between NPT *and Various Variables*

By linear correlation analysis of the test indexes of the PCOS group, the results showed that NPT was significantly positively correlated with FINS, TG, TC, WBC, N, CRP, IL-6, TNF-α. The results were shown in Table 6.

Table 6: Results of linear correlation analysis between NPT and each indicator.

Index	NPT	
	Correlation coefficient r	*P value*
FINS	0.649	<0.001
TG	0.315	<0.001
TC	0.321	<0.001
WBC	0.348	<0.001
N	0.357	<0.001
CRP	0.362	<0.001
IL-6	0.431	<0.001
TNF-α	0.374	<0.001

Multivariate Stepwise Regression Analysis of NPT *and Various Indicators*

In order to further analyze the correlation between NPT and various indicators, we used NPT as the dependent variable, and the other indicators as the independent variables. The sample data was used for multivariate stepwise regression analysis. The results suggested that among all the factors, the influence of FINS and IL-6 was the largest.

Discussion

PCOS is a syndrome with chronic inflammation as a key contributor to its pathogenisis. The essential inflammatory markers are WBC and CRP. A recent study found that the number of WBC, Neu and lymphocytes was higher in PCOS women than controls (P<0.05) [6]. Similarly, Rudnicka E, et al. [7] found WBC and CRP were significantly higher in the PCOS group. Özay AC et al. [8] also found patients with PCOS had significantly higher neutrophil count, neutrophil-lymphocyte ratio (NLR), platelet, platelet-lymphocyte ratio (PLR), plateletcrit (PCT) and C-reactive protein (CRP) values than normal women. The results of this study showed that compared with the non-PCOS group, the neutrophil and CRP

level of patients with PCOS increased, which is consistent with the above results. At the same time we found that the CRP of the obese people whether in the PCOS group or in the non-PCOS group were all significantly higher than those in the non-obese group. While the study of Tola E et al. [9] showed that serum NPT and CRP levels were significantly increased in nonobese adolescents and younger aged females with PCOS compared to healthy controls.

The chronic inflammatory processes are associated with an increase in the amount of inflammatory cytokines, including IL-1β, TNF-α, and IL-6. Ali DE et al. [10] showed that the levels of IL-6 and IL-18 were significantly increased in women with PCOS. Combination of metformin and pioglitazone therapy was more effective as compared to metformin alone in reducing the levels of IL-6 and IL-8 as well as insulin resistance in PCOS. It is speculated that IL-6 may be a factor that causes anovulation in PCOS patients. In addition, Bhatnager R et al. [11] found TNF-α levels between PCOS and control group were significant difference, which suggested TNF-α was one of the promising candidates for the marker of inflammation. In contrast to this finding, Brenjian S et al. [12] found after treatment with resveratrol, serum levels of IL-6, IL-1β, TNF-α, IL-18, NF-κB and CRP were all decreased. Nevertheless, there was no statistically significant decrease in serum levels of IL-6, TNF-α and IL-1β. The results of our present study showed that the levels of IL-6 in the PCOS group were significantly higher than those in the non-PCOS group ($p<0.05$), and the serum IL-6 in obese subjects were significantly higher than those in non-obese. While there was no significant difference of TNF-α between the PCOS group and non-PCOS group. It suggests that PCOS and obesity both are chronic subclinical inflammatory states, obesity is indispensable in the pathogenesis of PCOS, and it is speculated that PCOS patients are also more susceptible to diabetes and cardiovascular diseases including coronary heart disease.

It is reported that abnormal blood lipid metabolism is a separate and important factor in the pathogenesis of PCOS [13-15].The accumulation of fat and metabolism together with insulin resistance (IR) in PCOS patients, leads to a decrease in the breakdown of free fatty acids, which ultimately leads to an increase in the production of non-lipidated fatty acids, and an increase in the synthesis of TG and TC. Compared with the complications of PCOS patients with different BMI, the risk of obesity-induced hyperinsulinemia and diabetes is significantly higher in PCOS patients than in non-obese patients, which suggests a greater risk for obese PCOS patients [16]. The results of this study showed that there was no significant difference in fasting blood glucose (FPG) between the PCOS group and the non-PCOS group. While the serum TG and TC levels of PCOS were significantly higher than the non-PCOS group. The results also showed that compared with the non obese group, the level of TG in the obese group was more disorder ($P<0.05$), which indicated that BMI could be an independent factor affecting the metabolism of blood lipid in PCOS patients. Because the endocrine disorder in obese patients is more serious than that in non-obese patients, so it is suggested that in addition to the conventional symptomatic treatment and the drugs to reduce IR, it is necessary to carry out targeted weight loss treatment for obese PCOS, including adjusting their daily diet and exercising. Improving the sensitivity of insulin in the body can reduce the risk of long-term diabetes and cardiovascular disease.

Neopterin (NPT) is a kind of pterin compound with low molecular weight and a non-specific low molecular inflammatory marker. It is a specific marker for the enhancement of monocyte/macrophage activity induced by interferon gamma, reflecting lymphocyte-macrophage-mediated cellular immune activation markers [17]. It is mainly derived from the metabolism of guanosine triphosphate in the body. When the T cells are activated, interferon γ is released. Interferon γ acts on macrophages to activate them, and finally the activated macrophages synthesize and secrete NPT. Thus, NPT is also considered to be a specific product of macrophage activation. Since the amount of NPT produced by macrophages is related to its ability to release hydrogen peroxide, the level of NPT reflects the oxidative stress caused by activation of the immune system. NPT is stable in body fluids such as blood, cerebrospinal fluid and urine. It is not easily degraded in the body. Therefore, the degree of activation of the cellular immune system mediated by the "Lymphocyte- Macrophage Axis" in the body can be detected by measuring the NPT. Thus NPT is also considered to be a special marker, that is, NPT can prompt the activation of cellular immunity in the body [18].

Studies at home and abroad have shown that NPT is associated with various diseases activated by cellular immune responses, including infection, trauma, tumor, autoimmune, inflammatory response, etc. Recently some studies had shown that serum neopterin level was significantly higher in COVID-19 patients than the healthy controls. Neopterin levels perhaps can be used as an early prognostic biomarker for COVID-19 [19-21]. Nedeva I, et al. [22] found the levels of neopterin were significantly higher in patients with obesity and/or prediabetes and newly diagnosed diabetes than control group. At present, many studies tend to explore the correlation between NPT and atherosclerosis. Zembron-Lacny A, et al. [23] found NPT level in patients with peripheral artery disease differed significantly from reference group. Which indicate a crucial role of NPT in atheromatous process and its usefulness in monitoring peripheral artery disease severity. However, there is still relatively little research on the correlation between NPT and PCOS. Pourteymour Fard Tabrizi F et al. [24] found a significant improvement in neopterin, omentin-1 and chemerin by thylakoid-rich spinach extract supplementation was under the influence of weight change and insulin resistance status. The study of Tola E et al. [9] showed that serum NPT, CRP levels and lipid accumulation product index were significantly increased in nonobese adolescents and younger aged females with PCOS compared to healthy controls. NPT could be a predictive marker for elevated HOMA-IR index. In contrast to these findings, Agacayak E et al. [25] found no significant difference between patients with PCOS and control subjects in neopterin, IL-6, TNF-a and CRP levels. And no statistically significant difference was found between obese and

non-obese patients with PCOS and control subjects in neopterin levels. The results of our present study showed that the level of NPT in PCOS patients was higher than that of the control group, which was consistent with the study of Tola E et al. In addition, the level of NPT in obese PCOS patients was higher than that in non-obese patients ($P<0.01$). Combined with the results of this study, it is speculated that NPT may be an important indicator of changes in PCOS patients, and NPT is related to body mass index BMI. It is preliminarily speculated that there may be a certain correlation between NPT and PCOS. However, due to the small number of samples in this study, more samples need to be demonstrated.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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