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ORIGINAL ARTICLE

Evaluation of CRP/Albumin Ratio in Polycystic Ovarian Syndrome

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Abstract

Background Polycystic ovarian syndrome is a common endocrine disorder among women of reproductive age. It is characterized by menstrual abnormalities, hyperandrogenism and polycystic ovaries and can lead to many complications. Studies have postulated the role of inflammation in the pathophysiology of PCOS. As acute phase reactants often serve as markers of inflammation, this study aimed to evaluate the role of inflammatory markers in women with PCOS and healthy controls.

Material and Methods A total of 60 participants were enrolled; 30 cases of PCOS and 30 age matched healthy controls. Peripheral venous blood was collected for assessment of CRP, serum albumin, serum total testosterone, serum fasting insulin and fasting blood glucose, following which statistical analysis was done.

Results The CRP/albumin ratio was found to be significantly higher in women with PCOS as compared to healthy controls along with serum total testosterone and HOMA-IR. Correlation between CRP/albumin ratio and the levels of serum total testosterone and insulin resistance was found to be non-significant.

Conclusion An elevated CRP/albumin ratio in cases of PCOS compared to healthy controls supports the hypothesis of inflammation playing a key role in the pathophysiology of PCOS. CRP/albumin ratio can serve as a cheaper biochemical marker of the disease subject to further validation studies to establish its use in Indian population.

Keywords PCOS · CRP/albumin · Acute phase reactants · Inflammation

Background

Polycystic ovarian syndrome (PCOS) is a heterogeneous syndrome characterized by menstrual abnormalities, hyperandrogenism and polycystic ovaries and is also associated with insulin resistance and subsequent hyperinsulinemia [1]. With a prevalence ranging between 3.7 and 22.5% in the Indian population [2], it is not only the main causes of female infertility, but is also linked to other illnesses like cardiovascular problems, obesity, endometrial cancer, pregnancy issues, and type 2 diabetes mellitus [3].

Recent studies [4, 5] have highlighted the role of inflammation in the pathogenesis of PCOS with a study [6] reporting higher levels of inflammatory markers in cases of PCOS compared to healthy population (age and BMI matched). This has further prompted the postulation that PCOS may fundamentally be an inflammatory process leading to a state of chronic low-grade inflammation.

Acute phase reactants play an important role in inflammatory states and may even serve as clinical markers of inflammation. The liver produces and secretes C-reactive Protein (CRP), a positive acute phase reactant, in

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response to inflammatory cytokines. In addition to being a biomarker, CRP is thought to be a mediator of numerous inflammatory processes [7]. Increased CRP levels in women with PCOS have been seen in several studies [5, 6], and these levels were significant regardless of age or BMI. Contrarily, albumin is seen as a negative acute phase protein, and a reduction in albumin is a result of the body's reaction to inflammation.

According to a study [8], PCOS has a greater correlation with elevated CRP/albumin ratio than either hyperandrogenism or insulin resistance. Serum albumin is usually not considered during routine testing and diagnosis of PCOS; however, the study demonstrates that women with PCOS have lower albumin levels than controls. Excess adiposity is also linked to inflammation, but according to the study, the CRP/albumin ratio was elevated in diagnosed cases of PCOS irrespective of BMI. This emphasizes the crucial role inflammation is said to play in the pathogenesis of PCOS.

The following study aimed to evaluate the CRP/albumin ratio, serum total testosterone and insulin resistance in women diagnosed with PCOS, as well as in healthy population, and to study the association between CRP/albumin ratio and other established variables of PCOS, i.e. insulin resistance and serum total testosterone.

Materials and Methods

This study was a part of the ICMR STS programme. It was conducted in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynecology of a tertiary care centre from August to September 2022 in accordance with guidelines laid down in the Declaration of Helsinki. Participants were enrolled after Ethical clearance was obtained from the institutional ethics committee-human research (IECHR-2022-54-8-R1). Patients of PCOS were recruited from the Out Patient Department of Obstetrics & Gynecology, and healthy age matched volunteers were recruited from relatives visiting the hospital and supporting staff of the institute. Written informed consent was obtained from all participants.

Sample Size Calculation

Considering the CRP/albumin ratio as 0.53 ± 0.06 in PCOS group, we added 0.08 ± 0.02 in healthy control group [8]. Considering a mean difference $\alpha = 5\%$ and power = 90%, a sample of 10 subjects was required in each of two groups, i.e. women with regular menstrual cycles, and women diagnosed with PCOS. We recruited 30 participants in each group, i.e. a total of 60 subjects.

Participant Selection

Cases included newly diagnosed participants of PCOS in the age group of 20–40 years with normal BMI. A diagnosis of PCOS was made based on the Rotterdam diagnostic criteria [9], i.e. the presence of any two of the following: biochemical or clinical hyperandrogenism, ovulatory failure, or ultrasound-detected polycystic ovaries (12 or more small bubbles located circumferentially and/or ovarian volume > 10 mL). The presence of both hyperandrogenism and irregular menstrual periods eliminates the need for ultrasound in the diagnosis. Controls included women in the age group of 20–40 years with normal BMI with normal testosterone levels, and sample was taken in the follicular phase of their menstrual cycle.

Exclusion criteria were as follows: BMI less than 18 kg/m^2 or greater than 40 kg/m^2; use of oral contraceptive pills, steroids, or non-steroidal anti-inflammatory drugs (NSAIDs); hormonal imbalance including Cushing's syndrome and clinical or subclinical hyperthyroidism/hypothyroidism; diagnosed cardiovascular disorders, cancer, hepatitis, glomerulonephritis, inflammatory bowel disease or any other inflammatory condition.

Baseline Data Collection

History was elicited from the patient, following examination for details of severity of hyperandrogenism: grades of hirsutism (Ferriman-Gallwey scale), acne (Grades 1–4) and alopecia (the three-point Ludwig scale).

Biochemical Analysis

In all recruited subjects, 4 ml of peripheral venous blood was collected for assessing CRP, serum albumin, serum fasting blood glucose (FBG), serum fasting insulin and serum total testosterone.

CRP was estimated using RANDOX RX Imola Autoanalyzer (RANDOX, UK), serum albumin and fasting blood glucose were estimated using DXC 800 (Beckmann Coulter, USA), serum total testosterone was estimated using IMMULITE 2000 XPi (Siemens, Germany) immunoassay system, and fasting serum insulin was estimated using commercially available enzyme-linked immunosorbent assay kit (DRG International, USA).

Calculation of HOMA-IR and CRP/Albumin Ratio

Calculation of insulin resistance (HOMA-IR) was done using formula [10]. HOMA-IR = fasting plasma glucose (mmol/L) x fasting serum insulin (μIU/mL)/22.5.

CRP/albumin ratio was calculated as follows: CRP (mg/L)/albumin (gm/dL).

Statistical Analysis

Statistical analysis was performed using SPSS version 26 (SPSS Inc., USA). Values are represented as Mean ± Standard Deviation. Difference in variables between the two groups was compared by unpaired student t test or Mann–Whitney U test based on normality of data. Correlation analysis was done using Spearman Rho's correlation test. A p value < 0.05 was considered significant.

Observations and Results

A total of 60 participants were enrolled in the study: thirty cases of PCOS and 30 healthy age matched controls. The mean age was 23.80 ± 3.854 years in the cases of PCOS and 23.70 ± 3.941 in the healthy volunteers (Range: 18 to 32 years). Varying degrees of acne, alopecia and hirsutism were noted in 46.66%, 26.66% and 83.33% of PCOS patients, respectively.

Biochemical Parameters

Mean CRP, serum albumin and FBG levels are depicted in Table 1. A highly significant difference in CRP levels was noted between the two groups ($p < 0.001$).

Hormonal Parameters

Serum total testosterone and fasting serum insulin (FSI) levels are depicted in Table 2. A highly significant difference in serum total testosterone levels was noted between the two groups ($p < 0.001$), and a significant difference (0.002) in FSI was noted between the two groups.

CRP/albumin Ratio and Insulin Resistance

CRP/albumin ratio and HOMA-IR levels are depicted in Table 3. A highly significant difference in CRP/albumin ratio and HOMA-IR was noted between the two groups ($p < 0.001$).

Correlational analysis yielded a non-significant correlation between CRP/albumin ratio and serum total testosterone levels ($r = 0.182$ and $p = 0.165$), and a non-significant correlation is seen between CRP/albumin ratio and HOMA-IR ($r = 0.044$ and $p = 0.739$).

Discussion

Polycystic ovarian syndrome is a common endocrine disorder that affects women of reproductive age. Studies [4–6] have documented PCOS patients to have chronic low-grade inflammation, which increases their risk for diabetes mellitus, cardiovascular disease, and insulin resistance, among other conditions. Additionally, high androgen levels seen in patients of PCOS are postulated to exacerbate the low-grade inflammation via activation of mononuclear cells [11]. Therefore, this raises the question whether inflammation has a fundamental role to play in the pathophysiology of PCOS.

Table 1 Comparison of biochemical parameters among study groups

Analyte**	Case	Control	p value*
CRP (mg/L)	3.893 ± 2.718	2.000 ± 1.893	**< 0.001**
Serum albumin (g/dL)	4.100 ± 0.305	4.267 ± 0.449	0.098
FBG (mg/dL)	88.03 ± 6.840	85.33 ± 4.196	0.07

Bold indicate p values < 0.001 is highly significant

*The significance level is < 0.05, **values are expressed as mean ± SD

Table 3 Comparison of CRP/albumin ratio and HOMA-IR among study groups

Analyte**	Case	Control	p value*
CRP/albumin ratio	0.954 ± 0.691	0.480 ± 0.435	**0.001**
HOMA-IR	3.224 ± 1.403	2.217 ± 1.002	**0.001**

Bold indicate p values < 0.001 are highly significant

*The significance level is < 0.05, **values are expressed as mean ± SD

Table 2 Comparison of hormonal parameters among study groups

Analyte**	Case	Control	p value*
Serum total testosterone (ng/mL)	0.327 ± 0.0948	0.196 ± 0.009	**< 0.001**
Fasting serum Insulin (μIU/mL)	14.813 ± 6.785	10.413 ± 4.304	0.002

Bold indicate p values < 0.001 is highly significant

*The significance level is < 0.05, **values are expressed as mean ± SD

This study found CRP levels to be significantly higher in PCOS patients than healthy populations which is consistent with previous studies [5, 12]. CRP being a good marker of inflammation, supports the hypothesis that chronic low-grade inflammation contributes to the pathogenesis of PCOS. Additionally, it might explain why women with PCOS are more susceptible to cardiovascular diseases.

According to a recent study [8], serum albumin levels were shown to be lower in PCOS patients than in the general population. Albumin being a negative acute phase protein has been found to decrease as part of the body's response to inflammation, thus further supporting the role of inflammation in PCOS.

The study found significantly higher CRP/albumin ratio in PCOS patients as compared to healthy controls, similar to a prior study to assess CRP/albumin ratio in PCOS [8]. The hypothesis that PCOS is a chronic low-grade inflammatory state [4] is further supported by the fact that CRP/albumin ratio has been utilized in numerous studies as a prognostic score for other inflammatory disorders such as myocardial infarction [13], hepatocellular carcinoma [14] and small cell lung cancer [15]. Furthermore, given that it has previously been discovered that CRP/albumin ratio has a stronger correlation with PCOS than conventionally measured correlates like serum total testosterone and insulin resistance [8], this emphasizes the potential role of CRP/albumin ratio as a prognostic score for PCOS in the future.

In comparison with healthy controls, it was discovered that serum total testosterone, signifying hyperandrogenism, fasting blood sugar, fasting serum insulin, and HOMA-IR (insulin resistance) were all significantly higher in PCOS patients. It is established that PCOS causes hyperandrogenism and insulin resistance [1, 10, 16], and these symptoms were frequently utilized to make the diagnosis. Clinical manifestations like hirsutism, acne, and alopecia are brought on by hyperandrogenism, which also contributes to inflammation in PCOS.

CRP/albumin ratio and HOMA-IR as well as CRP/albumin ratio and serum total testosterone levels were not significantly correlated, according to correlational analysis. This might be explained by the study's small sample size.

Conclusion

An elevated CRP/albumin ratio in cases of PCOS compared to healthy controls supports the hypothesis of inflammation playing a key role in the pathophysiology of PCOS. CRP/albumin ratio can serve as a cheaper biochemical marker of the disease subject to further validation studies to establish its use in Indian population.

Limitations of the Study

The present study was done with a small sample size due to time and resources constraint. Studies with a larger sample size need to be done to determine the diagnostic value of CRP/albumin ratio in cases of PCOS and for better statistical accuracy.

Clinical Implications

The current approach to treating PCOS focuses primarily on symptom management, but identifying PCOS as an inflammatory process may have far-reaching effects on the disease's course, as addressing the inflammation in its early stages may help both prevent the onset of PCOS and advance our understanding of the condition. As CRP/albumin ratio is used as a prognostic score in various inflammatory conditions, it can also be used in the future to determine and evaluate the outcomes of polycystic ovarian syndrome.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics standard The study was done accordance with guidelines laid down in the Declaration of Helsinki. Participants were enrolled after Ethical clearance was obtained from the institutional ethics committee-human research (IECHR-2022-54-8-R1).

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