ASSOCIATION OF HIGH SENSITIVITY C-REACTIVE PROTEIN IN POLYCYSTIC OVARY SYNDROME

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Abstract

Objective: *This study is aimed to see the level of high sensitivity C-reactive protein (hs-CRP) and its association with manifestations of polycystic ovary syndrome (PCOS).*

Design: *This cross-sectional study was conducted over a period of one year (January 2017 to December 2018) in the department of Endocrinology of a University hospital.*

Participants: *Fifty-five PCOS patients diagnosed on basis of revised Rotterdam diagnostic criteria 2003 and 50 age-matched healthy controls [PCOS vs. Control- BMI (kg/m^2): 25.47±4.65 vs. 20.68±3.51, p<0.001].*

Main outcome measures: *hs-CRP level, manifestations of PCOS*

Methods: *After relevant history and physical examinations, blood was taken in fasting state during follicular phase of menstrual cycle to measure total testosterone (TT), luteinizing hormone (LH), follicle stimulating hormone (FSH) and hs-CRP. Hormones were measured by chemiluminescent microparticle immuno-assay and hs-CRP by nephelometric technique.*

Results: *hs-CRP (mg/L) was found significantly higher in PCOS patients [1.67 (0.69, 2.54) vs. 0.94 (0.30, 1.42), p=0.006] even after adjustment for age and BMI [OR (95% CI): 1.585 (1.093, 2.299), p=0.015]. Also hs-CRP status (>5 mg/L) was found significantly higher in them than that of controls; but only in non-obese (BMI <25 kg/m^2) participants [7.27% vs. 0.0%, p=0.018]. hs-CRP showed no significant correlation and predictive association with any of the manifestations of PCOS including age, BMI, waist circumference, TT and LH/FSH ratio [p=NS for all]*

Conclusions: *Patients with PCOS had significantly higher hs-CRP level and high hs-CRP status without any significant association with its manifestations.*

Key words: *polycystic ovary syndrome, high sensitivity C-reactive protein, body mass index, total testosterone*

DOI: https://doi.org/10.3329/jdmc.v30i2.56918
J Dhaka Med Coll. 2021; 29(2) : 142-148

Introduction

Polycystic ovary syndrome (PCOS), a common reproductive endocrinopathy, is associated with several clinical manifestations; despite being a common problem with many health hazards, its pathogenesis is still enigmatic.[1] A state of chronic low grade inflammation is thought to play critical role in the pathogenesis of insulin resistance followed by the cardio-metabolic manifestations in PCOS.[2] This metabolic meta-inflammation is mediated via adipocytes and their resident immune cells by secreting pro-inflammatory cytokines such as tumor necrosis factor- α and interleukin-6 (IL-6). IL-6 stimulates production

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Received: *24-01-2021* ***Revision:*** *17-02-2021* ***Accepted:*** *20-02-2021*

of C reactive protein (CRP) from different organ specific and vascular cells.[3,4] High sensitivity CRP (hs-CRP) is an analyte which can measure low level of inflammation with superior assay precision and accuracy along with better predictor of cardiovascular risk than other acute-phase reactants[5]. Adipocytes can also be a potential sites for androgen production. On the other hand, androgens can also trigger inflammation. The interactions among androgens, adipocytes and inflammation are still unresolved.[6] South Asian patients with PCOS present with more metabolic phenotype and are at increased risk of poor cardiovascular outcome[7]. However, data regarding the association of the manifestations of PCOS with inflammatory status among patients with PCOS from South Asian countries are limited especially from Bangladesh perspective. This study is aimed to see the inflammatory status by measuring hs-CRP and its associations with clinical and hormonal manifestations especially the diagnostic characteristics in patients with PCOS.

Materials and Methods

This cross-sectional study included 55 reproductive aged PCOS females (16 - 34 years) and 50 age-matched healthy controls [22.4±4.7 vs. 22.9±4, p=0.512]. Participants were enrolled consecutively by convenient sampling from the department of Endocrinology Bangabandhu Sheikh Mujib Medical University (BSMMU) over a period of one year. The study protocol was approved by institutional review board, BSMMU (*No.BSMMU/2017/292*). Informed written consent was taken from each participant before enrollment.

The PCOS patients were diagnosed according to revised 2003 Rotterdam consensus diagnostic criteria from any two criteria out of three: oligo or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries along with exclusion of other related etiologies[8]. Patients with primary amenorrhea, previous diagnosis of diabetes mellitus, history of intake of oral contraceptive, glucocorticoids, metformin, drugs with androgenic property, anti-obesity or ovulation inducing drugs within previous six months were excluded. Patients having thyroid function abnormality, hyperprolactinemia, non-classic congenital adrenal hyperplasia, androgen producing tumor were also excluded. Apparently healthy females with regular menstrual cycle without significant hirsutism and known endocrine disorders were included as control. History, physical examination including height, weight, waist circumference (WC), blood pressure (BP), hirsutism (by modified Feriman-Gallwey score, mFG) and acne were noted and blood was drawn for measurement of TT, TSH, prolactin (PRL) and hs-CRP from each participant and luteinizing hormone (LH), follicle stimulating hormone (FSH) in only PCOS patients in fasting state during follicular phase of menstrual cycle. Trans-vaginal or lower abdominal ultrasonography (USG) was done in only PCOS patients depending on marital status during follicular phase of menstrual cycle also.

All the hormones were analyzed by chemiluminescent microparticle immunoassay. Serum levels of hs-CRP were measured by a nephelometric technique (N high sensitivity CRP, Dade Behring) with intra-assay and inter-assay co-efficient of variation of 4.1-7% and 6-9.2% respectively.

Body mass index (BMI) e”25 kg/m^2, WC e”80 cm, systolic BP e”130 mm-Hg or diastolic BP e”85 mm-Hg, modified F-G score e”8, hs-CRP >5.0 mg/L, TT >46.0 ng/dl and LH/FSH ratio >2.0 were considered as general obesity, central obesity, elevated BP, significant hirsutism, high hs-CRP, hyperandrogenemia and altered LH/FSH ratio respectively[9-14]. Any ovarian volume >10 ml was taken as polycystic ovarian morphology (PCOM)[1].

All data were expressed as mean (± SD) [age, age of menarche, BMI, WC, systolic and diastolic BP and TT] or median (inter-quartile range, IQR) [modified F-G score, TSH, prolactin, hs-CRP and LH/FSH ratio] or frequency (percentages, %) [personal and family history and other clinical and biochemical statuses] depending on their types and distribution. Associations between groups were done by independent-samples t-test or Mann-Whitney U test or Chi-square/ Fisher’s exact test as appropriate. Correlations of hs-CRP with clinical and biochemical variables were done by Spearman’s correlation

test. Predictive association of hs-CRP with PCOS or its manifestations were analyzed by multivariate linear and binary logistic regression analyses. Any p value <0.05 was considered as statistically significant.

Results

The characteristics of the study population are shown in Table 1. Almost all (94.5%) patients with PCOS had irregular menstruation. PCOS patients had significantly higher percentages of personal history of MR/abortion [14.5% vs. 0.0%, p=0.006] and subfertility [21.8% vs. 0.0%, p<0.001] than healthy control. Percentages of family history were present significantly higher in PCOS group than control group [menstrual disturbance: 49.1% vs. 4.0%, p<0.001; hirsutism: 23.6% vs. 0.0%, p<0.001; PCOS: 38.2% vs. 0.0%, p<0.001; subfertility: 23.6% 2.0%, p=0.001]. Patients with PCOS had significantly higher BMI (kg/m^2) [25.47±4.65 vs. 20.68±3.51, p<0.001], WC (cm) [83.24±11.05 vs. 70.96±6.60, p<0.001], systolic BP (mm-Hg) [110.18±13.81 vs. 103.80±11.76, p=0.013], modified F-G score [8.0 (6.0, 10.0) vs. 2.0 (2.0, 3.0), p<0.001] with higher percentages of acne [50.9% vs. 0.0%, p<0.001] than control. TSH (mIU/ml) [2.25 (1.72, 3.02) vs. 1.57 (1.11, 2.45), p=0.001], TT (ng/dl) [68.20±33.58 vs. 31.49±13.22, p<0.001] and hs-CRP (mg/L) [1.67 (0.69, 2.54) vs. 0.94 (0.30, 1.42), p=0.006] levels were significantly higher and prolactin level (ng/ml) [8.44 (5.78, 13.66) vs. 14.14 (10.08, 18.44), p<0.001] was significantly lower in PCOS group than control group. More than 80% patients with PCOS had PCOM.

Table-II

Characteristics of the study population with hs-CRP status (N= 105)

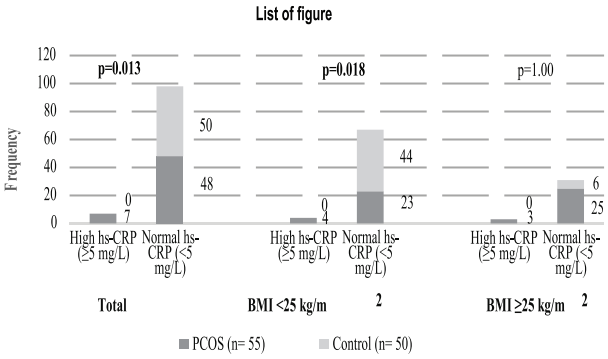
Variables	PCOS (n= 55)	Control (n= 50)	p
Personal history			
Age of menarche, year	12.95±1.21	12.84±0.93	0.620
Irregular menstruation	52 (94.5)	0 (0.0)	<0.001
MR/abortion	8 (14.5)	0 (0.0)	0.006
Subfertility	12 (21.8)	0 (0.0)	<0.001
Family history			
Menstrual disturbance	27 (49.1)	2 (4.0)	<0.001
Hirsutism	13 (23.6)	0 (0.0)	<0.001
PCOS	21 (38.2)	0 (0.0)	<0.001
Subfertility	13 (23.6)	1 (2.0)	0.001
Physical findings			
BMI, kg/m^2	25.47±4.65	20.68±3.51	<0.001
WC, cm	83.24±11.05	70.96±6.60	<0.001
Systolic BP, mm-Hg	110.18±13.81	103.80±11.76	0.013
Diastolic BP, mm-Hg	71.82±10.38	68.40±8.66	0.069
Modified F-G score	8.0 (6.0, 10.0)	2.0 (2.0, 3.0)	<0.001
Acne	28 (50.9)	0 (0.0)	<0.001
Investigation findings			
hs-CRP, mg/L	1.67 (0.69, 2.54)	0.94 (0.30, 1.42)	0.006
TSH, μIU/ml	2.25 (1.72, 3.02)	1.57 (1.11, 2.45)	0.001
Prolactin, ng/ml	8.44 (5.78, 13.66)	14.14 (10.08, 18.44)	<0.001
TT, ng/dl	68.20±33.58	31.49±13.22	<0.001
LH/FSH ratio	1.98 (1.37, 3.0)	Not done	–
PCOM	45 (81.8)	Not done	–

Data were presented as mean±SD of median (IQR) or frequency (%) as appropriate
Independent-samples T test or Mann-Whitney U test or Chi-square/Fisher's exact test was done as appropriate

Figure 1 is showing hs-CRP status of the study population. PCOS patients had significantly higher frequency of high hs-CRP status (>5 mg/L) [12.7% vs. 0.0%, p=0.013] than control. None of the healthy control had high level of hs-CRP. When the study population was divided by BMI, the significance remained positive only in nonobese (BMI <25 kg/m^2) group [100% vs. 34.33%, p= 0.018].

Table II is showing that hs-CRP had significant predictive association with PCOS even after adjustment for age and BMI [OR (95% CI): 1.585 (1.093, 2.299), p=0.015].

Among the manifestations of PCOS, only patients with centrally obesity had significantly higher hs-CRP level than those without central obesity [2.1 (0.96, 2.69) vs. 1.06 (0.35, 1.99), p=0.017] (Table 3). However, in multivariate



Chi-square/ Fisher's exact test was done. Within parentheses are percentages over respective study group

Fig-1: *hs-CRP status in the study population with obesity*

Table-II

Association of hs-CRP level with PCOS by binary logistic regression

Covariates	Odds ratio (95% confidence interval)	p*
hs-CRP, mg/L	1.585 (1.093, 2.299)	**0.015**
Constant	0.007	0.004

*Age and BMI adjusted

Table-III

hs-CRP level in different manifestations of PCOS

Variables	Category	No.	hs-CRP (mg/L) median (IQR)	p
Menstrual cycle	Irregular	52	1.67 (0.69, 2.32)	0.903
	Regular	3	2.54 (0.21)	
Body mass index	Obese (e"25 kg/m^2)	28	2.05 (0.84, 2.70)	0.141
	Nonobese	27	1.48 (0.41, 2.21)	
Waist circumference	Centrally obese (e"80 cm)	33	2.1 (0.96, 2.69)	**0.017**
	Nonobese	22	1.06 (0.35, 1.99)	
Blood pressure	Elevated (e"135 or e"85 mm-Hg)	7	2.12 (1.67, 2.32)	0.405
	Normal	48	1.60 (0.66, 2.65)	
Hirsutism	Significant (mFGS e"8)	38	1.60 (0.70, 2.37)	0.716
	Insignificant	17	1.95 (0.52, 2.89)	
Acne	Present	28	1.76 (0.72, 2.31) [28]	0.743
	Absent	27	1.67 (0.65, 2.69) [27]	
Biochemical androgen status	Hyperandrogenemia (>46 ng/dl)	41	1.63 (0.67, 2.50)	0.657
	Normoandrogenemia	14	1.84 (0.84, 2.71)	
LH/FSH ratio	Altered (>2.0)	27	1.48 (0.52, 2.54)	0.743
	Normal	28	1.91 (0.72, 2.59)	

Mann-Whitney U test was done

Table-IV

Correlations and linear regression analyses of hs-CRP as dependent variable in patients with PCOS

Determinants of 'r'	Spearman's correlation		Linear regression	
	r	p	β	p
Age, years	0.043	0.754	-0.011	0.945
BMI, kg/m^2	0.110	0.424	0.097	0.392
Waist circumference, cm	0.153	0.264	-0.189	0.460
Systolic BP, mm-Hg	-0.051	0.711	0.184	0.473
Diastolic BP, mm-Hg	-0.047	0.734	0.011	0.964
Modified Ferriman-Gallwey score	0.066	0.633	-0.118	0.493
Total testosterone, ng/dl	0.112	0.417	-0.005	0.979
LH/FSH ratio	-0.074	0.592	-0.009	0.954
Constant			B= 1.365	0.795

r= correlation co-efficient; β= standardized linear regression co-efficient

binary regression model, central obesity had no significant predictive association with hs-CRP [OR (95% CI): 1.211 (0.811, 1.808, p=0.350; constant: OR: <0.001, p=0.001] when adjusted for age and BMI. Similarly, hs-CRP level (mg/L) across the phenotypes of PCOS were statistically similar [phenotype A (38, 69.1%) vs. phenotype B (9, 16.4%) vs. phenotype C (3, 5.5%) vs. phenotype D (5, 9.1%): 1.65 (0.70, 2.40) vs. 1.20 (0.43, 4.18) vs. 2.54 (0.21) vs. 1.86 (1.09, 2.75), p=0.973] (not shown in table).

hs-CRP had either no significant correlation nor linear association with any of the manifestations of PCOS [p=NS for all] (Table 4). Similarly in multivariate regression analysis also showed that, age [OR (95% CI): 0.988 (0.814, 1.198), p=0.99], obesity [2.311 (0.171, 31.266), p=529], central obesity [7.617 (0.438, 132.528), 0.164], elevated BP [4.732 (0.321, 69.749), p=0.258], significant hirsutism [1.336 (0.090, 19.885), p=0.833, presence of acne [2.263 (0.295, 17.333), p=0.432], hyperandrogenemia [0.537 (0.073, 3.977), p=0.543], altered LH/FSH ratio [1.870 (0.318, 10.985), p=0.489]] and PCOM [0.268 (0.027, 2.684), p=0.262] had no predictive associations [constant: OR=0.017, p=0.428] with high hs-CRP status in patients with PCOS (not shown in table).

Discussion

The aim of this study was to determine hs-CRP level and status along with its relations with characteristics in PCOS patients. We found significantly higher level of hs-CRP in PCOS patients even after adjustment for age and BMI along with significantly higher frequency of high hs-CRP status than control. However, we did not find any significant associations of hs-CRP with manifestations of PCOS or its phenotypes.

Only 12.7% patients with PCOS had high hs-CRP. Previous study found higher frequency of elevated hs-CRP by using the same cut-off used in our study.[12] This difference is probably due to a different population. The findings also indicates that PCOS is a state of low grade inflammation.

The level of hs-CRP in patients with PCOS is controversial. However, most of the studies found significantly higher level in PCOS than control. Two meta-analyses also showed around two folds increase of hs-CRP in PCOS than control.[15,16] We also found significantly higher level of hs-CRP in PCOS than control. Several environmental factors (diet, physical activities, smoking status, etc), genetic polymorphisms affecting hs-CRP level along with phenotypic differences in different studies are thought to contribute to different observations.[12,17,18]

We also found significantly higher level of hs-CRP in PCOS than control even after adjustment

for age and BMI. This finding is consistent with other studies.[16,19] The hs-CRP status was significant only in non-obese patients with PCOS. Obesity is a recognized state of inflammation. So higher level of hs-CRP is attributed to PCOS independent of obesity. Besides, hs-CRP level was also statistically similar between obese and non-obese patients with PCOS in our study. Furthermore, weight loss in patients with PCOS is associated with a slower reduction of hs-CRP than control[20]. Presence of PCOS in a patient with obesity further increases the inflammatory status. So, hs-CRP may not be a good marker of inflammation in obese PCOS patients.

We did not find any associations of clinical or biochemical androgen status with hs-CRP in patients with PCOS. Similar findings were also observed by others.[19,21] Similarly, the association of hs-CRP with free testosterone in PCOS was also found controversial.[22,23] So, the association between testosterone and hs-CRP still remains inconclusive. We did not find significant association between LH/FSH ratio with hs-CRP in PCOS patients. Samy et al (2009) and Rudnicka et al. (2020) also did not find significant association between hs-CRP with LH or FSH in patients with PCOS.[24,25] So, inflammation seems to be less important in the pathogenesis of PCOS. Rather, PCOS precedes the development of chronic inflammation leading to endothelial dysfunction, insulin resistance, atherosclerosis and predisposes PCOS patients to atherosclerotic cardiovascular disease in future.

There are several limitations of our study. The sample size was small. Besides, we could not measure free testosterone or sex-hormone binding globulin, genetic polymorphisms affecting hs-CRP level and other inflammatory markers.

Conclusion

PCOS is characterized by modest increase of hs-CRP irrespective of age and BMI. However, this low grade inflammation has no association with the characteristic features as well as phenotypes of PCOS. Further study should look at the association of cardiovascular risk factors with hs-CRP in patients with PCOS.

Declarations

Ethics approval and consent to participate

The study protocol was approved by institutional review board of Bangabandhu Sheikh Mujib Medical University (*No.BSMMU/2017/292*). Informed written consent was taken from each participant.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

Partial funding from University Research and Development, BSMMU

Acknowledgement

We are grateful to Department of Microbiology & Immunology and Biochemistry & Molecular Biology for their support for hormonal and biochemical analyses.

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