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Research Article

High sensitivity C - reactive protein (hs-CRP) and clinical characteristics, endocrine, metabolic profile in Indian women with PCOS: a correlation

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ABSTRACT

Background: Role of hs-CRP was studied in PCOS women.
Methods: Correlation between serum hs-CRP and endocrine, metabolic profile was studied in 30 healthy women and 88 PCOS women. In PCOS women correlation between hs-CRP and clinical characteristics viz obesity, infertility, acne, hirsutism, acanthosis nigricans (AN) was also studied. Serum levels of hs-CRP, Luteinizing hormone (LH), Follicle stimulating hormone (FSH), LH:FSH ratio, Testosterone (Testo), fasting insulin, fasting blood glucose (FBG), total cholesterol (TC), triglyceride (Tg), low density lipoprotein (LDL), high density lipoprotein (HDL) and Homeostasis Model Assessment (HOMA) were estimated.
Results: Mean serum hs-CRP in PCOS women was higher than that in control women (6.9 ± SE 0.84 v/s 2.0 ± SE 0.19mg/L, P=0.005). In PCOS group overweight/obese had higher hs-CRP as compared to normal weight women (P=0.0051). In control group hs-CRP was positively correlated with age (r=0.385 p=0.035) and LDL (r=0.38 P=0.036). PCOS women showed positive correlation between hs-CRP and cholesterol, LDL, fasting insulin, HOMA. PCOS women showed a significant negative correlation between hs-CRP and LH. AN positive PCOS women showed higher serum hs-CRP levels as compared to AN negative PCOS women (11 ± SE 0.7 v/s 5.5 ± SE 2.3, P=0.0439).
Conclusions: Serum hs-CRP is raised in Indian PCOS women reflecting association of low grade chronic inflammation. A positive correlation is present between hs-CRP and AN, insulin in PCOS women and obesity may aggravate this association. A positive correlation between hs-CRP and TC, LDL in the background of normal lipid profile is suggestive of precedence of chronic inflammation over dyslipidemia in PCOS.

Keywords: PCOS, Obesity, Hirsutism, Acanthosis nigricans, hs-CRP

INTRODUCTION

High sensitive CRP (hs-CRP) synthesized by the liver is a marker of low-grade chronic inflammation. Low-grade chronic inflammation in turn is a key process in the development of atherosclerosis and high hs-CRP level is independent cardiovascular risk factor.[1,2] An association between raised hs-CRP and Insulin resistance has been proven.[3,4] Polycystic ovary syndrome (PCOS) is a common endocrinological disorder. Irregular menses, infertility, hyperandrogenism (HA), Acanthosis nigricans (AN) characterize this complex syndrome. Obesity is common in PCOS. PCOS women often show presence of insulin resistance and are at high risk of metabolic syndrome (MS), NIDDM.[5] Women with PCOS have significantly increased serum hs-CRP concentrations relative to those in healthy women with normal menstrual rhythm and normal androgens. A low grade chronic

inflammation as a novel mechanism contributing to the increased risk of chronic heart disease and type 2 diabetes mellitus (T2DM) in these women has been proposed.[6] It has been proposed that chronic inflammation might be more important to the pathogenesis of type 2 diabetes in women compared with men and the relation between hs-CRP and diabetes remains strong in women than in men.[7] With this background the present research work was conducted to study correlation between hs-CRP and clinical characteristics, endocrine and metabolic profile in Indian PCOS women.

METHODS

This prospective study was carried out over the period of two years. Newly diagnosed 88 post pubertal PCOS women of reproductive age consulting endocrinology hospital for the complaints of irregular menses and/ or infertility, acne and hirsutism and 30 apparently healthy women as control were enrolled in the present study. The diagnosis of PCOS was fulfilled as per Rotterdam criteria.[8] Presence of at least two criteria from clinical, hormonal and abdominal USG category was considered diagnostic of PCOS. Women with complaint of irregular menses or oligomenorrhea (absence of menses for 35-182 days) or amenorrhea (absence of menses for >182 days), signs or symptoms of HA, abdominal USG showing at least 12 follicles (2-9 mm in diameter) arranged peripherally around a dense core of ovarian stroma or scattered throughout an increased amount of stroma were enrolled in the study. Patients having any other major systemic illness including systemic inflammatory diseases, congenital adrenal hyperplasia, hyperprolactinemia, acromegaly, functional hypothalamic amenorrhea were excluded. The study was approved by Institutional Ethics committee. All the guidelines of Declaration of Helsinki were followed.

Detailed menstrual history, marital status, parity were recorded in both the groups. PCOS women were clinically examined. The study subjects were investigated for the endocrine and metabolic parameters viz. Serum levels of hs-CRP, Luteinizing hormone (LH IU/L), Follicle stimulating hormone (FSH IU/L), LH:FSH ratio, Testosterone (Testo, ng/ml), fasting blood glucose (FBG mg%), fasting insulin (mU/ml), total cholesterol (TC mg/dl), triglyceride (Tg mg/dl), low density lipoprotein (LDL mg/dl), high density lipoprotein (HDL mg/dl). In the control group the investigations were done from 6th to 12th day of menstrual cycle. This was not possible in PCOS women because of irregular menses. Cut-off of BMI as Standard Consensus Statement for Indian population was considered i.e. Normal BMI: 18.0-22.9 kg/m^2, Overweight: 23.0-24.9 kg/m^2 Obesity: >25 kg/m^2 BMI ≥25 was considered as obese.[9] hs-CRP levels were considered as low (less than 1.0 mg /L), moderate (1.0 to 2.9 mg/ L), and high (at least 3.0 mg /L).[10] Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as marker of insulin resistance. HOMA value >1.9 was considered as presence of insulin resistance.

Assay methods

In vitro quantitative determination of hormones was carried by electrochemiluminescence immunoassay method (Roche- Hitachi Cobas e 411). Blood glucose was measured on autoanalyser (Vital Scientific Microlab 300) using oxidase method. Serum hs-CRP levels (enzyme linked immunoturbidometric assay method) and lipid profile was estimated by quantitative enzymatic colorimetric method (GPO-PAP methodology) using Agappe diagnostic kits.

Statistical tests and data analysis

Data was analyzed using software (Graph pad prism version 5.02). .Comparison between proportions was analyzed by Fischer's exact test. Intergroup data was compared by nonparametric – Mann Whitney U test. Correlation was analyzed by Spearman test. P value less than .05 was considered significant.

RESULTS

Mean hs-CRP levels differed in control women and PCOS women. In control women with high hs-CRP levels; the elevation was marginal with a range of 3.1-3.6mg/L. In PCOS women with high hs-CRP levels; the range was 3-43.2mg/L. In the control group hs-CRP was positively and significantly correlated with age (r= 0.39, P=0.0353). However, in PCOS women hs-CRP was insignificantly correlated with age (r=0.1820, P=0.0897).

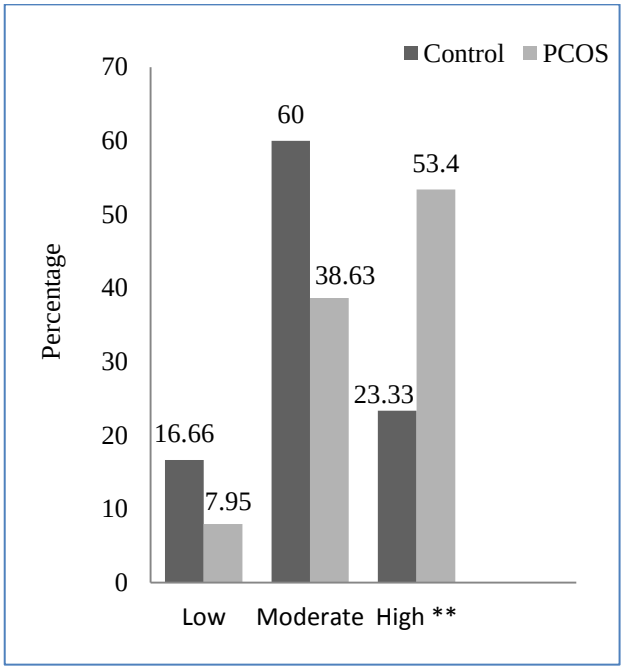

Figure 1: Comparison between percentage of control and PCOS women showing low, moderate and high hs-CRP levels.

p value ** highly significant

Table 1: Comparison of age and serum hs-CRP levels in control and PCOS women.

		hs-CRP(mg/L)		
	Age (years)	**Total / overall**	**Non-obese**	**Overweight / obese**
Control	20.73 ± 0.38	2.01 ± 0.19 (n=30)	1.9 ± 0.20 (n=26)	2.66 ± 0.56 (n=4)
PCOS (n=88)	22.83 ± 0.47	6.9 ± 0.84 (n=88)	3.6 ± 0.61 (n=30)	8.6 ± 1.2 (n=58)
p value	0.0608	0.0005**	0.2215	#

n= number of subjects, **highly significant, #Sample size less. Values as mean ± SE

Table 2: Comparison between hs-CRP levels in PCOS patients showing different clinical characteristics.

Clinical characteristics	Status	n	hs-CRP (mg/L)	p value
BMI	Normal weight	30	3.6 ± 0.61	0.0043**
	Overweight / obese	58	8.6 ± 1.2	
Infertility (married)	Absent	19	12 ± 2.2	< 0.0001***
	Present	32	4.4 ± 1.2	
Acne	Absent	74	6.9 ± 0.91	0.5878
	Present	14	7.0 ± 2.2	
Hirsutism	Absent	52	6.8 ± 1.1	0.9594
	Present	36	7.0 ± 1.3	
AN	Absent	64	5.5 ± 0.7	0.0439*
	Present	24	11 ± 2.3	

n=number of patients, *significant, **, ***highly significant. Value of hs-CRP is shown as mean ± SE

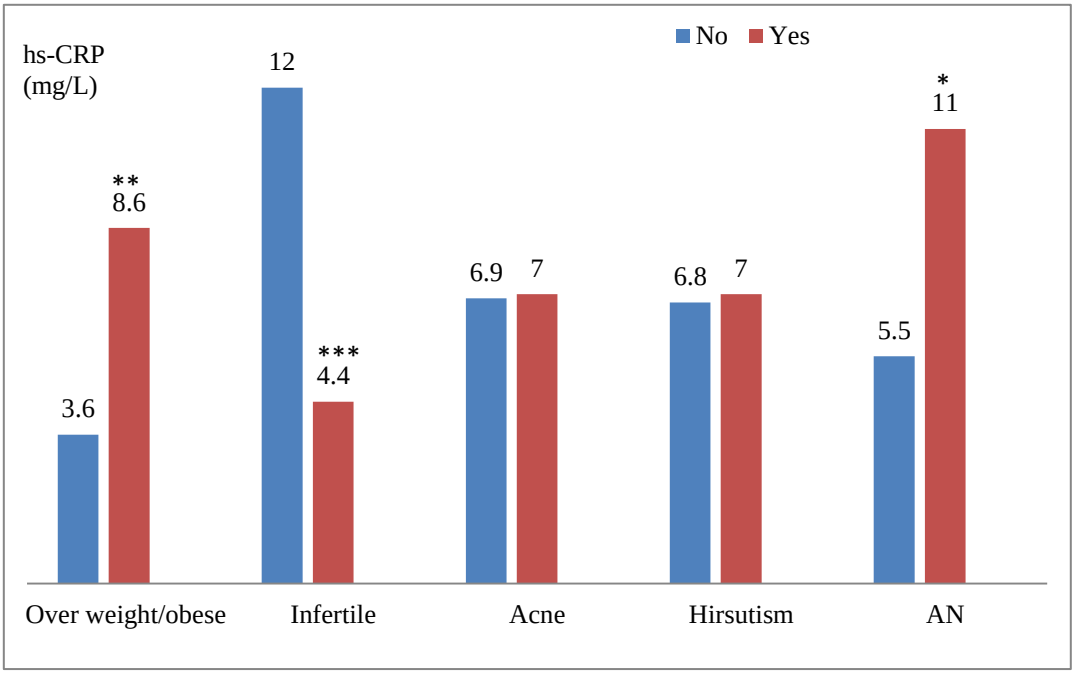

Figure 2: Comparison between hs-CRP levels in PCOS patients showing different clinical characteristics.

p value *significant, **, ***highly significant.

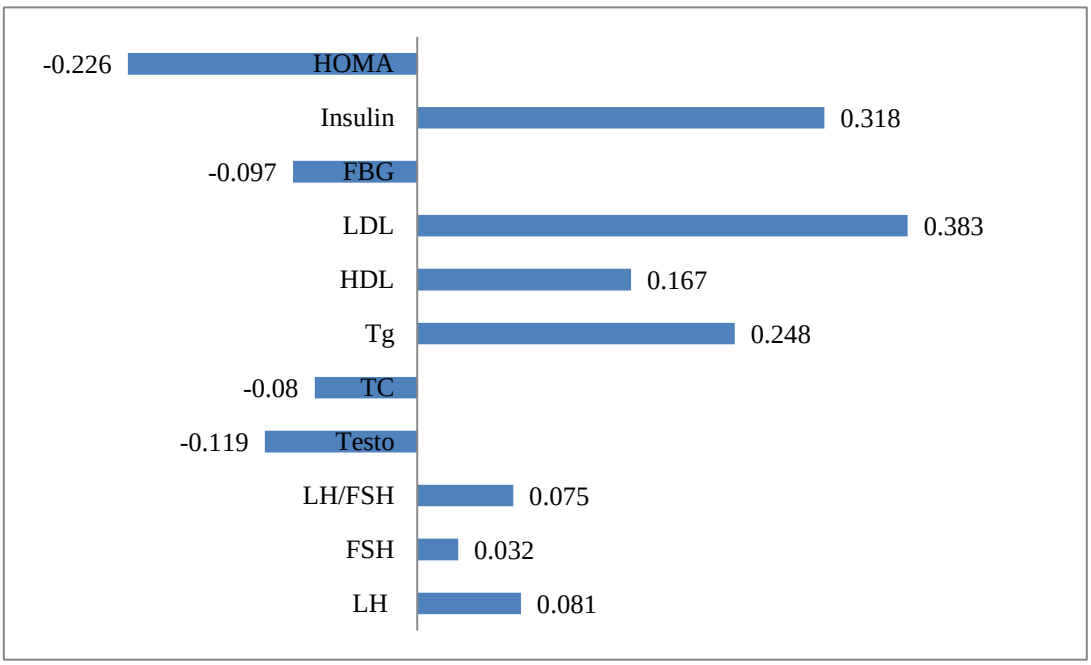

Figure 3: Correlation between serum hs-CRP and endocrine, metabolic profile in control group (n=30).

r values, * p value significant.

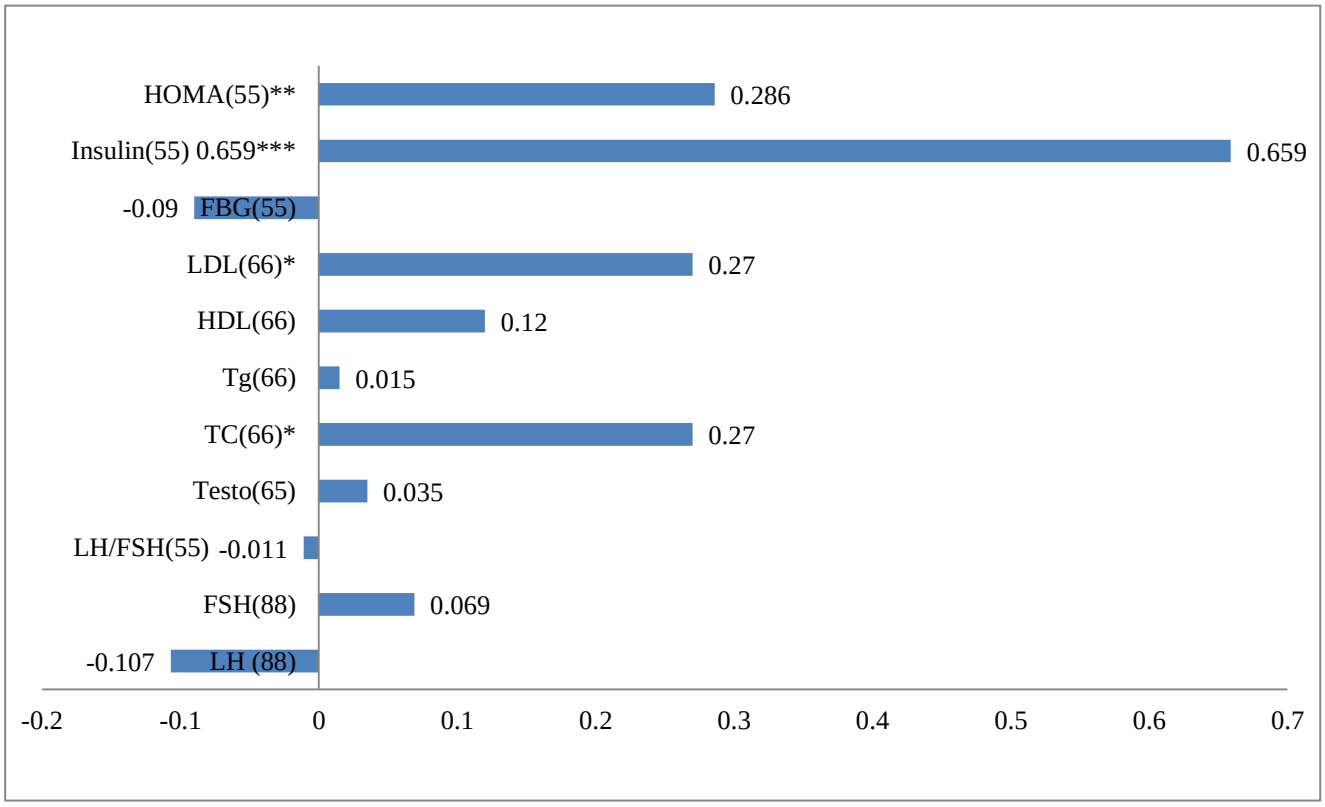

Figure 4: Correlation between serum hs-CRP and endocrine, metabolic profile in PCOS women.

r values
Figures in parenthesis=number of subjects, p value *significant, **, ***highly significant

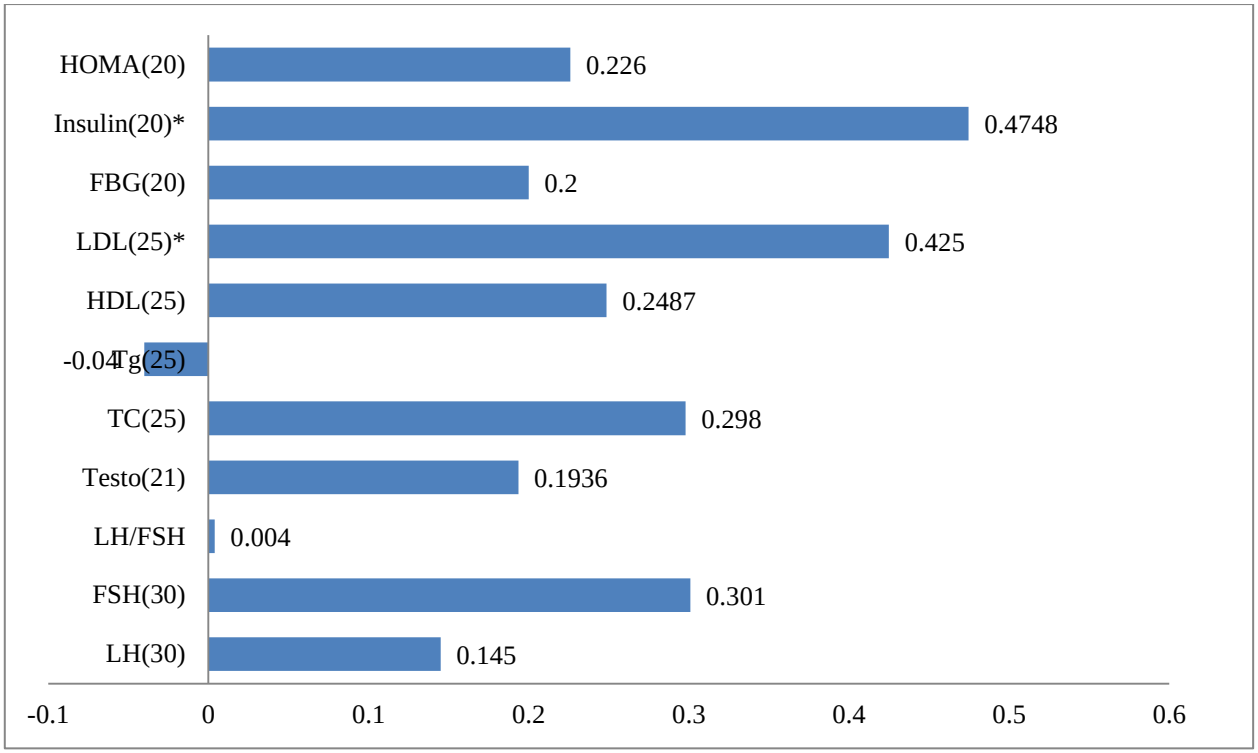

Figure 5: Correlation between serum hs-CRP and endocrine, metabolic profile in non-obese PCOS women.

r values
Figures in parenthesis =number of subjects, * p value significant

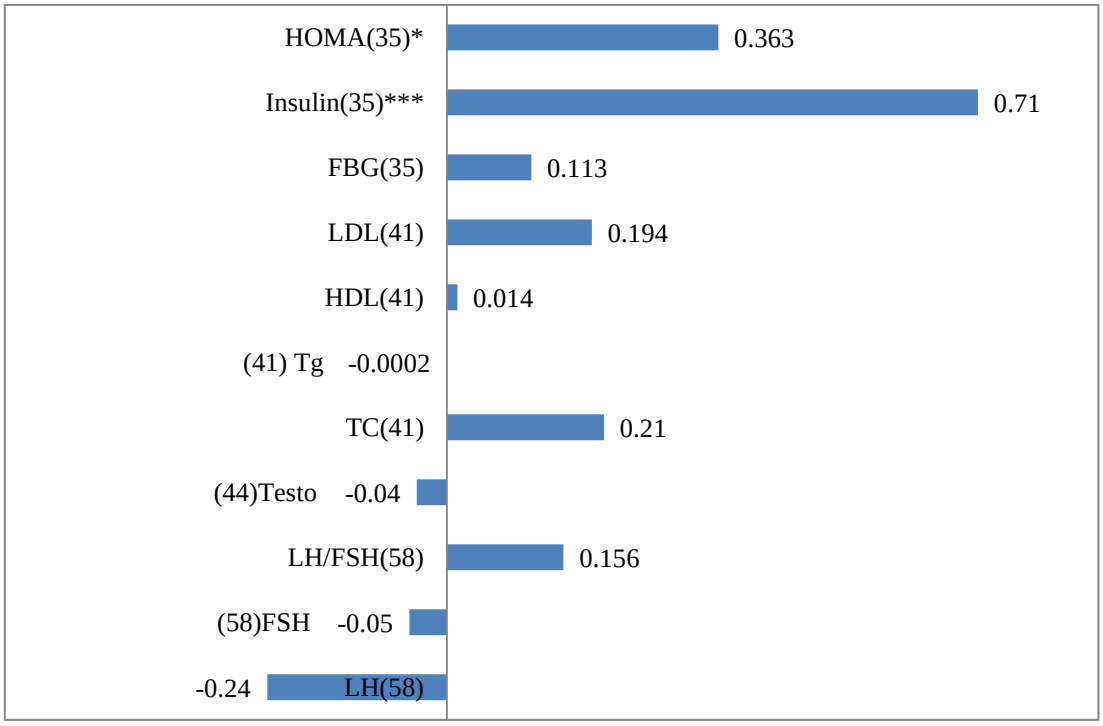

Figure 6: Correlation between serum hs-CRP and endocrine, metabolic profile in overweight/obese PCOS women.

r values
Figures in parenthesis =number of subjects, p value *significant, *** very highly significant.

DISCUSSION

The present study shows high prevalence of raised serum hs-CRP levels in Indian PCOS women (Table 1, Figure 1). The highly significant difference between the mean serum hs-CRP levels in non PCOS controls and PCOS women indicates association of chronic low-grade inflammation in PCOS patients. This observation is in accordance to the previous studies. Flavia Tosi et al. had reported increased hs-CRP in PCOS women .The authors have concluded PCOS is accompanied by a low-grade chronic inflammation.[11] Héctor F. Escobar-Morreale et al. have reported a two times increase in hs-CRP levels in PCOS women.[12] PCOS women with CRP concentrations greater than 3 mg/L had a higher prevalence of moderate cardiovascular risk compared with BMI-matched controls.[10] The prevalence of Indian women with PCOS in the present study showing hs-CRP levels more than 3 mg/L is alarming (Figure 1). A positive correlation between hs-CRP and age implies early intervention in the diseases associated with chronic inflammation including PCOS is highly desirable.

In the present study hs-CRP levels in normal weight PCOS women did not differ significantly from normal weight control women (Table 1). Higher level of hs-CRP was observed in overweight/obese PCOS women as compared with normal weight PCOS women and the difference was highly significant (Table 2, Figure 2). Data of obese women in PCOS group and obese women in the control group was not compared because of the inadequate number of obese control women. Nonetheless the results indicate that the chronic inflammation in PCOS could be because of or is accentuated by increased body weight. Raised hs-CRP in PCOS is attributed to obesity in some of the previous studies. A positive relation between hs-CRP and obesity has been reported. The study conducted by A. Elisabeth Hak, indicated that in healthy, middle-aged women, CRP was strongly associated with measures of obesity and CRP was associated with BMI.[13] Lifestyle interventions such as exercise and weight loss are effective in lowering CRP and other inflammatory markers.[14] Obesity plays a significant role in PCOS. Weight reduction in PCOS has beneficial effects and has been shown to improve free androgen levels; insulin sensitivity and ovulatory function.[15] Thomas A. Pearson et al in recommendations for Clinical and Public Health Practice related to cardiovascular diseases (CVD) have suggested that hs-CRP levels may be useful in motivating patients to improve lifestyle behaviors. The authors have also mentioned that the benefits of this strategy remain uncertain.[16] The result of present study supports previous findings of relation between obesity and high hs-CRP in PCOS women. Future interventional studies in PCOS women involving weight reduction, its beneficial effects and association with hs-CRP if any, are needed.

PCOS woman may present with complain of infertility. In the present study married fertile and infertile PCOS women showed significant difference in the mean hs-CRP levels (Table 2, Figure 2). This finding may be attributed to high ratio of obese/overweight to normal weight women in fertile group (15 v/s 4 respectively) as against in infertile group (29 v/s 20). The mean age of fertile PCOS women was significantly more than that of the infertile PCOS women (27.53 ± 3.93 v/s 23.84 ± 3.28, p=0.0016). This may also be the reason of higher hs-CRP in fertile PCOS women. Role of hs-CRP in infertility in PCOS if any cannot be explained on the basis of result of the present study. Further studies involving age and weight matched fertile and infertile PCOS women are needed. Sarah Robinson et al in a preliminary study on correlation of baseline hs-CRP and *in vitro* fertilization (IVF) outcome had reported that, baseline hs-CRP is of no use as predictive marker of IVF outcome in routine clinical practice. Their study was conducted in non PCOS women.[17]

In the current study hs-CRP levels in PCOS women with acne and without acne did not differ. hs-CRP levels were comparable in hirsute and nonhirsute PCOS women (Table 2, Figure 2). On stratifying the data of PCOS group in to normal weight and overweight/obese, hirsute overweight/obese women (n=25) showed significantly higher hs-CRP levels (8.7 ± 1.7 SE v/s 3.1 ± 1.0 SE, p=0.0090), as compared to hirsute normal weight women (n=11).This result endorses association of chronic inflammation with obesity rather than that with hirsutism.

Control subjects in the present study showed insignificant inverse correlation between hs-CRP and testosterone (Figure 3). Androgen may have a protective role in preventing raise in hs-CRP levels.[10] In PCOS women no significant correlation was observed between hs-CRP and testosterone (Figure4). Ji Young Oh et al. in the study on serum hs-CRP levels in normal weight PCOS did not observe any association between hs-CRP and free testosterone levels.[18]

Acanthosis nigricans, a marker of insulin resistance is seen in some PCOS patients. Table 2 and Figure 2 show that the PCOS women with AN had higher mean hs-CRP levels as compared to those without AN. This difference was significant. Raised hs-CRP is associated with insulin resistance as reported previously.[19] In a previous study a positive correlation between AN and obesity in PCOS has been reported.[20] The correlation between AN and hs-CRP observed in the present study to some extent may be because AN is common in obese PCOS. We are not aware of previous studies on relation between clinical features of PCOS viz hirsutism and hs-CRP.

In both the control and PCOS women serum hs-CRP level was not correlated with the fasting blood glucose. (Figure 3 and 4). In the control group the correlation between hs-CRP and fasting insulin, HOMA was negative and did not reach the level of significance. The negative correlation may be because of euinsulinemia with persistence of insulin sensitivity in healthy women. PCOS women had a highly significant positive

correlation between hs-CRP and fasting insulin, HOMA (Figure 4). In PCOS group the association between serum levels of hs-CRP and insulin, HOMA is stronger in overweight/obese women as compared to normal weight women (Figure 5 and 6). Previous studies have shown that both lean and obese PCOS women are at risk of either impaired glucose tolerance (IGT) or T2DM and general screening of PCOS patients for IGT and/or T2DM has been recommended.[21-23] Early screening and intervention can reduce the burden of treatment of type 2 DM. Though Fasting glucose is an easy parameter to be investigated for, a substantial proportion of PCOS women with IGT or even T2DM show normal fasting glucose concentrations.[24] Oral Glucose Tolerance Test (OGTT) is relatively time consuming and less suitable as a screening tool. A positive correlation between hs-CRP and fasting insulin as well as HOMA can be considered for identifying PCOS women who are at high risk of IGT and/or T2DM. The current result substantiates interrelation between PCOS, IR and chronic inflammation. Monitoring of hs-CRP levels can even assist in evaluating response to drug treatment and can be used as a prognostic tool.

The control group shows insignificant positive correlation between hs-CRP and gonadotropins (Figure 3). Figure 4 shows PCOS women in the present study had insignificant inverse correlation between serum hs-CRP and LH levels. On stratifying the data into normal weight and overweight/obese PCOS women, normal weight PCOS women showed insignificant positive correlation and overweight/obese PCOS women showed inverse correlation between hs-CRP and LH levels (Figure 5 and 6). Morales et al. have shown that LH pulse frequency was accelerated in both lean and obese PCOS, whereas the mean 24-h LH pulse amplitude was increased in lean but not in obese PCOS patients.[25] McCartney et al. in the study in pubertal girls have reported that obesity in prepubertal and early pubertal girls is associated with reduced LH secretion and reduced nocturnal changes of LH. In latter pubertal girls, obesity is linked with reduced LH amplitude but elevated LH frequency; the latter may reflect effects of hyperandrogenemia.[26] Association of raised hs-CRP, and obesity, reduced LH amplitude in obesity and the inverse relation observed between hs-CRP and LH in the current study call for further studies in this direction. Optimum secretion and functioning of gonadotropin is essential for normal ovulatory cycles. Chronic inflammation may play a role in the pathophysiology of PCOS leading to disrupted gonadotropin secretion resulting into anovulatory cycles. We are not aware of previous studies reporting the inverse relation between serum hs-CRP and LH in PCOS women.

Figure 3 shows significant positive correlation between serum hs-CRP and LDL levels in control subjects indicating association of this cytokine with lipid metabolism. In addition to LDL, PCOS women showed positive correlation between serum hs-CRP and total cholesterol (TC) (Figure 4). In PCOS the mean serum cholesterol and LDL were in normal range. This together with raised hs-CRP and a positive correlation indicates that chronic inflammation may precede deranged lipid profile in PCOS women. It has been reported that the C-reactive protein level is a stronger predictor of cardiovascular events than the LDL cholesterol level and that it adds prognostic information to that conveyed by the Framingham risk score. Umed A. Ajani et al. reported a crude prevalence 28.8% of high CRP concentration among those with an overall normal lipid profile.[27] Paul M. Ridker et al. in a prospective study evaluated prediction value of 12 plasma variables as cardiovascular risk factors. The authors have concluded that hs-CRP proved to be the strongest and most significant predictor of the risk of future cardiovascular events.[28] With this knowledge and normal serum LDL, Cholesterol, raised hs-CRP in PCOS women observed in the current study it can be suggested that investigating PCOS women for the latter parameter is valuable.

CONCLUSIONS

Serum hs-CRP levels are raised in Indian PCOS women as compared to apparently healthy Indian women reflecting association of low grade chronic inflammation with this disorder. Obese PCOS women are more prone for raised hs-CRP. A positive correlation is present between hs-CRP and AN, insulin levels in PCOS women and obesity may aggravate this association. In addition to raised hs-CRP levels, a positive correlation between hs-CRP and TC, LDL in the background of normal lipid profile is suggestive of precedence of chronic inflammation over dyslipidemia in PCOS. Correlation of hs-CRP with age warrants an early detection and intervention in disorders related to chronic inflammation including PCOS. Considering the value of hs-CRP in predicting risk for cardiovascular diseases and its association with Insulin resistance, investigating PCOS women for serum hs-CRP may have a prognostic value and further studies involving more number of subjects are needed.

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Ethical approval: The study was approved by the institutional ethics committee

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