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Original Research Article

Study of D Dimer, Lipid Profile, High Sensitivity C-Reactive Protein in Relation to Anthropometric Measurements in PCOS Patients

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Abstract

Introduction: Polycystic Ovarian Syndrome (PCOS) is a heterogeneous, multifactorial and polygenic condition affecting adult females characterised by increased androgen production in the ovaries. The criteria require presence of any two conditions out of the given following three: (a) Oligomenorrhea/ anovulation, (b) Clinical/ biochemical hyperandrogenism and (c) Polycystic ovaries (≥12 follicles in each ovary measuring 2–9 mm). Symptoms like hirsutism and irregular menstrual bleeding, anovulation frequently occurs during puberty time. D-dimer reflects human fibrinolytic activity and is considered to be an important biomarker of hyper-coagulability. C-Reactive Protein (CRP) is a type of protein produced by the liver that serves as an early marker of infection or inflammation.

Aim: To study D Dimer, Lipid profile, High Sensitivity C-Reactive Protein (hs-CRP) in relation to anthropometric measurements in PCOS patients of Government General Hospital, Ananthapuramu, and to compare with controls. To determine the correlation between Triglycerides, hs-CRP and D-dimer with respect to BMI.

Materials & Methods: 105 female patients attending the outpatient department of Obstetrics and Gynaecology at Government General Hospital, Ananthapuramu, Andhra Pradesh, during the study period from March 2023 to September 2023 diagnosed with PCOS were studied.

Results: Cases having BMI ≥ 25, have increased levels of hsCRP, D dimer, triglycerides when compared with cases having BMI < 25 and healthy controls. Triglycerides, hs-CRP and D-dimer levels were also positively correlated to each other.

Conclusion: Triglycerides, hs-CRP and D-dimer levels were positively correlated to each other, indicating that there is an interrelationship between hypertriglyceridemia, chronic subclinical inflammation and hypercoagulability in PCOS, which may contribute to intensify the atherogenic and thrombogenic profile. If not addressed or targeted for treatment in early stages it might lead to complications related to pregnancy and its outcome, as well as cardiovascular diseases and type 2 Diabetes mellitus.

Keywords: PCOS, hs-CRP, D-dimer, BMI.

Introduction

Polycystic Ovarian Syndrome (PCOS) is a heterogenous, multifactorial and polygenic condition affecting adult females characterised by increased androgen production in the ovaries which was originally described in the year 1935 by Stein and Levinthal as syndrome that is manifested by amenorrhea, hirsutism and obesity associated with enlarged ovaries [1,2]. The etiology of this heterogeneous condition remains obscure. ESRHE /ASRM Rotterdam consensus meeting 2003 are useful in the diagnosis of PCOS. The Rotterdam's criteria require presence of any of the following two conditions out of below three:(a) Oligomenorrhea/ anovulation, (b) Clinical biochemical hyperandrogenism, (c) Polycystic ovaries (≥12 follicles in each ovary measuring (2–9mm). Symptoms like hirsutism and irregular menstrual bleeding, anovulation occurs during puberty time [3]. Lipid abnormalities may trigger platelet activation, activate the coagulation pathway, and inhibit fibrinolysis and are associated with Coronary Vascular Disease risk. Coagulation and fibrinolysis occur together for the hemostatic balance in the organism thus blood can flow normally through arteries and veins. To avoid exaggerated blood clotting, the fibrin clot is degraded by plasmin, resulting in formation of fibrin degradation products such as D-dimer [4,5,6]. D-dimer can be evaluated,

as it reflects human fibrinolytic activity and is considered to be an important biomarker of hypercoagulability [7]. C-Reactive protein (CRP) is a type of protein produced by the liver that serves as an early marker infection or inflammation [8]. Inflammation is an uninterrupted effect of the atherosclerotic process, which promotes the formation of the lipid stria [9,10]. High sensitivity C reactive protein (hs-CRP) is the biomarker of chronic subclinical inflammation and is associated with the risk of cardiovascular diseases [11]. CRP concentration increases with increase in inflammation or tissue damage, making it a useful marker for monitoring disease severity [12-16]. Recently several biochemical markers have been introduced to predict the vascular events in PCOS. Of these, the role of hsCRP in PCOS is gaining increasing interest [17]. Increased BMI and visceral adiposity in PCOS women is a cause for Low grade chronic inflammation and hypercoagulable state in recent studies [18]. PCOS is one of the most common causes of infertility. PCOS women has many ongoing cardio metabolic risk factors, suffer from obesity, diabetes, which worsen metabolic and fertility outcomes but the metabolic syndrome in nulliparous women cannot be neglected as it is involved in long term risk for cardiovascular morbidity limited research is available about PCOS in nulliparous women prior to attaining parity. Hence this study is planned to explore and analyse different biochemical parameters such as D Dimer, lipid profile, hs CRP in nulliparous women with PCOS with BMI ≥25.

Aim & Objectives: To study D dimer, lipid profile, Hs CRP in relation to anthropometric measurements in PCOS patients of Government General Hospital, Ananthapuramu, and to compare with controls. To determine the correlation between Triglycerides, hsCRP and D-dimer, BMI.

Materials and Methods

Patients attending the outpatient department of Obstetrics and Gynaecology at Government General Hospital, Ananthapuramu, Andhra Pradesh, during the study period from March 2023 to September 2023 diagnosed with PCOS were studied after obtaining informed and written consent. A total of 105 female patients were included in this study which was approved by Institutional Ethics Committee.

Ultra-sonography of abdomen and pelvic – USG was also performed in all the subjects to diagnose and rule out PCOS.

Inclusion Criteria: Nulliparous women of 18 to 40 years age group with PCOS according to the criteria of Rotterdam - presence of two conditions out of the following three:

1. Oligomenorrhea/anovulation,
2. Clinical/biochemical hyperandrogenism and
3. Polycystic ovaries (≥12 follicles in each ovary measuring 2–9 mm) were included in cases and Normal Nulliparous women with matched reproductive age group as controls.

Exclusion Criteria:

1. Age group less than 18 years and more than 40 years.
2. Participants with h/o pregnancy /parity/living children.
3. Participants who had previously diagnosed & treated or on treatment for PCOS.
4. Participants with Thyroid dysfunction, Diabetes mellitus, Hyperprolactinemia
5. 5.Patients not giving consent for research.

Sample Collection: Peripheral venous blood sample was collected from all the study subjects after overnight fasting and transferred into a tube containing anticoagulant (sodium citrate). Plasma was immediately separated by centrifugation at 2000 rpm for 10 min, analysed for D dimer on AU 480 auto Analyzer of Beckmann Coulter. Serum was separated and analysed for hs-CRP and lipid profile. The separated plasma was transferred into aliquots and stored at −50°C until further analysis for estimation of D-dimer. The tests were done on AU 480 auto Analyzer of Beckmann Coulter using kits.

Serum total cholesterol by cholesterol esterase oxidase peroxidase, triglycerides by glycerol -3 phosphate oxidase peroxidase, HDL cholesterol by CHOD -POD method. Hs-CRP and D dimer were estimated by Immunoturbidometric method.

Statistical Analysis: All data were collected, tabulated and analysed using Microsoft excel software. Data obtained was expressed as mean ± standard deviation. Difference in all biochemical parameters studied among study groups was tested using independent samples t-test. The associations between Triglycerides, BMI, hs-CRP and D-dimer in PCOS patients were analyzed using Pearson correlation co-efficient, 'r' value and 'P' value were calculated using SPSS-25. A P value of <0.05 was considered as statistically significant.

Results

The total participants in our study were 105 nulliparous adult women out of which 35 with BMI ≥ 25, 35 with BMI < 25, 35 were healthy controls.

AGE: The mean age of the nulliparous women cases with BMI ≥ 25 was 20.5 ± 1.90 years, with BMI < 25 was 20.7 ± 1.98 and in healthy participants the mean age was 20.5 ± 1.87 years indicating age matched controls.

BMI: Taking the weight &height of each participant, BMI was estimated using the formula BMI= Weight (kgs) / Height (m^2).

The mean ± SD of various parameters studied and results obtained are tabulated in Table no-1 below.

Table 1: Demographic profile of the study subjects

Parameter	Cases (n=35) BMI ≥ 25 Mean ± SD	Cases (n=35) BMI < 25 Mean ± SD	Controls (n=35) Mean ± SD	p-value
Age group - years	20.5 ± 1.90	20.7 ± 1.98	20.5 ± 1.87	0.863; NS
BMI (kg/m^2)	28.7 ± 1.42	21.8 ± 1.96	22.2 ± 1.35	<0.001; S
Waist circumference-cms	85.9 ± 1.96	75.0 ± 1.34	74.2 ± 1.84	<0.001; S
Hip circumference-cms	103.6 ± 3.46	89.7 ± 1.56	80.5 ± 2.63	<0.001; S

*NS = Not Significant; S = Significant; SD = Standard deviation

Table 2: hs-CRP and D-dimer lipid profile among the study group and control group.

Parameter	Cases (n=35) BMI ≥ 25 Mean ± SD	Cases (n=35) BMI < 25 Mean ± SD	Controls (n=35) Mean ± SD	p-value
Hs-CRP (mg/L)	5.57 ± 0.49	1.89 ± 0.23	0.40 ± 0.11	<0.001; S
D dimer(mg/L)	2.41 ± 0.57	1.32 ± 0.12	0.15 ± 0.06	<0.001; S
Total Cholesterol (mg/dL)	217.2 ± 40.72	155 ± 30.12	117 ± 20.9	<0.001; S
Triglycerides (mg/dL)	168 ± 21.6	159 ± 16.2	123 ± 12.1	<0.001; S
HDL (mg/dL)	46.3 ± 12.3	45.2 ± 9.1	44.7 ± 6.86	<0.001; S
LDL (mg/dL)	140 ± 37.6	128 ± 32.3	99.2 ± 22.9	<0.001; S

*NS = Not Significant; S = Significant; SD = Standard deviation

Hs-CRP, D dimer, triglycerides, HDL, LDL were found to be significantly elevated ($p < 0.001$) in Cases with BMI≥25, when to compared to cases with BMI < 25 and healthy controls.

Table 3: Correlation between Triglycerides, hs-CRP & D-dimer, BMI

Correlation between	Pearson's Correlation coefficient (r)	p-value
Triglyceride and hs-CRP	0.602	<0.001; S
Triglyceride and D-dimer	0.733	<0.001; S
hs-CRP and D-dimer	0.900	<0.001; S
BMI and Triglyceride	0.413	<0.001; S
BMI and hs-CRP	0.843	<0.001; S
BMI and D-dimer	0.701	<0.001; S

Correlation between Triglycerides and hs-CRP shows strong positive correlation between them with a correlation coefficient, $r = 0.602$ and were significant statistically ($p < 0.001$). Correlation between Triglycerides & D-dimer shows strong positive correlation between them with a correlation coefficient, $r = 0.733$ and were statistically significant ($p < 0.001$). Correlation between BMI and Triglycerides shows moderate positive correlation and, $r = 0.413$ and were statistically significant ($p < 0.001$). Correlation between BMI and hs-CRP & D-dimer shows strong positive correlation between them and were significant statistically. Correlation between hs-CRP & D-dimer shows moderate positive correlation, with a correlation coefficient, $r = 0.900$ and were statistically significant ($p < 0.001$). the correlation is depicted in the figure 1. Below

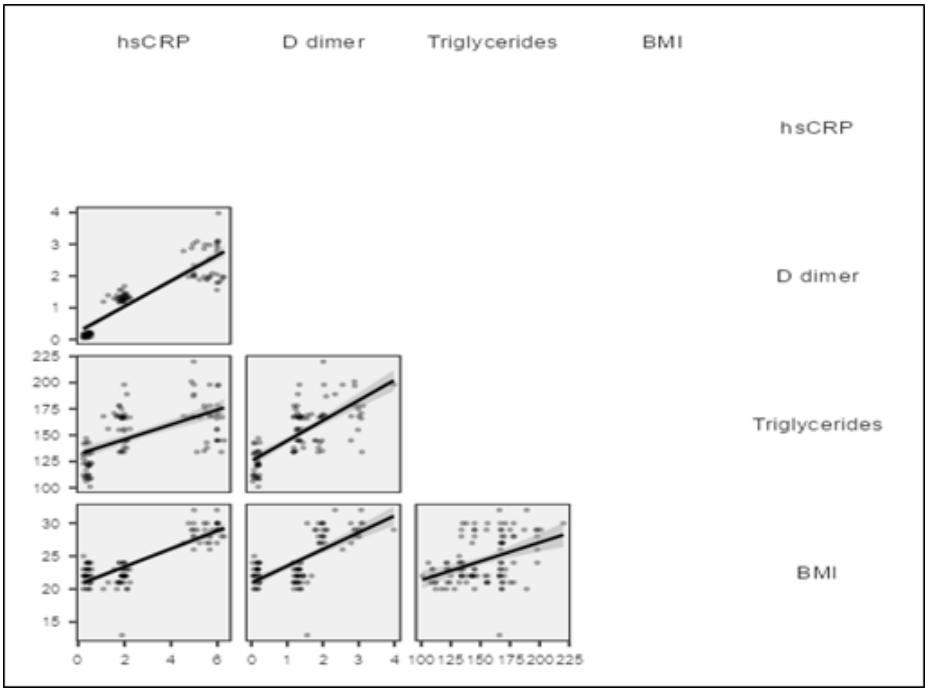

Figure 1: Correlation between Triglycerides, hs-CRP and D-dimer with respect to BMI and among themselves.

Discussion

Polycystic ovary syndrome (PCOS) is a syndrome that can be presented with amenorrhoea, hirsutism and obesity. PCOS is a multifactorial and polygenic condition. PCOS is seen most commonly in young women. In our study hs-CRP, significantly elevated ($p < 0.001$) in Cases having BMI≥ 25, when compared to cases with BMI < 25 and healthy controls. Elevated levels of inflammatory mediators in women with PCOS have suggested that PCOS is characterized by low-grade chronic inflammation is indicative of future development of cardiovascular disease [19]. Sumithra CN. et al study found that low grade chronic inflammation is an independent marker of CVD and is demonstrated by persistently elevated serum hs-CRP [20]. CRP selectively binds to the oxidised LDL molecules and is deposited in the atheromatous plaques and contributes to the pathogenesis and progression of the atheroma due to its pro inflammatory property [21]. Triglycerides, HDL, LDL were found to be significantly elevated ($p < 0.001$) in PCOS Cases with BMI≥ 25, when compared to PCOS cases having BMI < 25 and healthy controls. The higher risk of cardiovascular events has been associated with changes in lipid metabolism through the modification of low-density lipoprotein (LDL) and high-density lipoprotein cholesterol (HDL-C) levels [22]and the chronic subclinical inflammation [23]. In addition, they act like procoagulant agents, favouring a hypercoagulability state, and then raising the risk of thrombo-embolic diseases [24]. Lipid abnormalities may trigger platelet activation, activate the coagulation pathway & inhibit fibrinolysis and are consequently associated with CVD [25,26]. Several studies of dyslipidemia and PCOS have reported an atherogenic lipid profile, predominantly increased TG and decreased HDL-C levels [27]. BMI found to be significantly elevated ($p<0.001$) in PCOS cases compared to controls. High BMI is another factor that contributes to the development of inflammation. Adipocytes secrete about 25 % of IL-6 which can stimulate the release of CRP from the liver [28]. A study by Visser M et al reported higher prevalence of low-grade systemic inflammation in overweight and obese individuals compared with normal weight persons [29]. D-dimer, found to be significantly elevated ($p < 0.001$) in Cases with BMI > 25, when compared cases having BMI < 25 and healthy controls in PCOS patients indicates hypercoagulability state in PCOS patients. Correlation between Triglycerides and hs- CRP & Triglycerides and D-dimer shows strong positive correlation between them with a correlation coefficient, $r = 0.602$ and were significant statistically ($p<0.001$). These relationships may indicate that the increase in the levels of triglycerides in PCOS patients may contribute to intensify the sub-clinical inflammation process and hypercoagulability state. A Positive correlation between hs- CRP and D-dimer was also observed, which suggests an inter-relationship between chronic sub-clinical inflammation and hyper coagulability. Pro-inflammatory mediators can stimulate the expression of coagulant molecules and inhibit the anticoagulant and fibrinolytic pathways, while components of activated hemostatic system can stimulate the production of pro-inflammatory cytokines [30]. Therefore, there is bi-directional

relationship between inflammation and hypercoagulability. Correlation between BMI and hs- CRP which is a predictor of cardiovascular risk & D-dimer which is a biomarker of hypercoagulability shows strong positive correlation between them. Correlation between BMI and Triglycerides indicates that there is an interrelationship between hypertriglyceridemia, chronic sub- clinical inflammation and hypercoagulability in PCOS patients, which may contribute to intensify the atherogenic and thrombogenic profile.

Conclusion

To conclude the findings of the present study, shows that patients with PCOS of BMI > 25 have increased hs- CRP and D- dimer, Triglycerides when compared to controls, these parameters being readily available can be used as predictor of inflammation and hypercoagulation in PCOS patients thus aiding in early diagnosis and necessary intervention. Triglycerides, hs- CRP D-dimer and BMI levels were also positively correlated to each other indicating that there is an inter relationship between hypertriglyceridemia, chronic subclinical inflammation and hypercoagulability in PCOS, which may contribute to intensify the atherogenic and thrombogenic profile. This study reiterates that Hypercoagulable state and low-grade inflammation in PCOS are an attribute of metabolic defect in it. If not addressed or targeted for treatment in early stages it might lead to complications related to pregnancy and its outcome, as well as cardiovascular diseases and type 2 Diabetes mellitus.

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