DYSLIPIDEMIA, SERUM TESTOSTERONE AND BODY MASS INDEX IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME -A CROSS SECTIONAL ANALYSIS

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Background: Polycystic ovary syndrome (PCOS) is a heterogeneous, multifactorial endocrinopathy in women of reproductive age characterised by the ovarian manifestation of multiple metabolic abnormalities primarily anovulation, hyperandrogenism, and/or polycystic ovary shape.

Aim: To assess the relation between body mass index and serum lipid profile and the relation between body mass index and serum testosterone in PCOS women and to correlate body mass index, serum lipid profile and serum testosterone in women with PCOS.

Methodology: Population based cross-sectional study carried out in a tertiary care hospital among 100 consecutive women diagnosed as having PCOS in the reproductive age group. The biochemical estimation of the lipid profile was done using digital Photocolorimeter and the estimation of serum testosterone was done in Minividas machine.

Results: There is a highly significant difference in BMI level between the Lean and Obese PCOS women with $p<0.01$. The obese PCOS category of women has lower mean score of the parameter High Density Lipoprotein than their lean counterparts. There was a highly significant difference in Triglyceride level between the Lean and Obese PCOS women with $p<0.01$. In the parameter Testosterone (ng/ml), though the mean scores of both the groups are found to be slightly higher than the normal value but, the difference is not statistically significant ($p>0.05$).

Conclusion: The results corroborated that PCOS raises the risk of cardiovascular disease and metabolic yndrome by promoting the development of an atherogenic lipid profile. Additionally, it supports the hypothe sis that PCOS and hyperandrogenism are linked, regardless of the patient's BMI.

Key- words: Polycystic ovary syndrome, PCOS, Serum testosterone, Serum lipid profile.

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INTRODUCTION:

Polycystic ovary syndrome (PCOS) is a heterogenous, multifactorial endocrinopathy in woman of reproductive age characterised with the ovarian expression of various metabolic disturbances, mainly characterised by anovulation, hyperandrogenism and/or polycystic ovary morphology.

PCOS is one of the most common endocrine disorders in women of reproductive age, affecting 5% to 10% of women worldwide. [1] This familial disorder appears to be inherited as a complex genetic trait. [2] Stein and Leventhal in the year 1935, described an association between the presence of bilateral polycystic ovaries and signs of amenorrhea, oligomenorrhea, hirsutism, and obesity. [3]

A. Criteria for the Definition of PCOS according to ESHRE/ASRM Statement [4,5]

1. Oligo-ovulation or anovulation (e.g., amenorrhea, irregular uterine bleeding)
2. Clinical and/or biochemical signs of hyperandrogenism (e.g., hirsutism, elevated serum total or free testosterone)
3. Polycystic ovaries (by ultrasonography). The existence of 12 or more follicles measuring 2 to 9 mm in diameter or an increased ovarian volume (>10 mL) are required by the sonographic criteria for PCO. A single ovary meeting these criteria is PCO diagnosis

B. Criteria for the Diagnosis of PCOS according to AES (2006) [6]

To include all of the following:

1. Hyperandrogenism: hirsutism and/or hyperandrogenaemia
2. Ovarian dysfunction: oligo-anovulation and/or polycystic ovaries
3. Exclusion of other androgen excess or related disorders.

Hyperandrogenism is the key feature of PCOS, resulting primarily from excess androgen production in the ovaries and, to a lesser extent, in the adrenals. [7] Biochemical evidence of hyperandrogenism is based on the finding of elevated circulating androgen concentrations. Testosterone is the most important androgen produced by the ovary and the usual basis for diagnosis of hyperandrogenaemia. Most women with PCOS have high testosterone levels.

The free testosterone level is more sensitive for diagnosis of hyperandrogenic disorders. [8] Clinical evidence of hyperandrogenism includes hirsutism, acne, and androgenic alopecia, all of which relate to the effect of androgens on the pilosebaceous unit. Because the sensitivity of the pilosebaceous unit varies significantly among individuals, the correlation between these clinical features and biochemical measures of hyperandrogenism is relatively poor. [9,10]

Julian H. Barth et al studied the association of body mass index and biochemical hyperandrogenaemia in women with and without PCOS. They concluded a strong correlation exists between BMI and FAI but not with total testosterone, possibly due to the mediation of SHBG. With rising BMI, hyperandrogenaemia in the form of androstenedione appears to be enhanced in PCOS. However, a direct causal link between BMI and Androgenaemia has not been found. [11]

Obesity occurs in more than 50% of patients with PCOS. Obesity in women with PCOS typically is distributed centrally, with a greater increase in visceral than in subcutaneous fat. [12,13,14,15] Among women with PCOS, there is widespread variability in the degree of adiposity by geographic location and ethnicity. [16,17,18]. Perhaps the most prevalent metabolic aberration seen in PCOS patients is dyslipidemia. Applying the National Cholesterol Education Program guidelines, nearly 70% have at least one borderline or elevated lipid level [19], although many women with PCOS have entirely normal lipid profiles. [20,21,22,23]

N. Swetha et al analysed and correlated the biochemical parameters (Glucose, Magnesium, Uric Acid and lipid profile) in women with PCOS. PCOS women had higher BMI ($P < 0.0001$) with increased total cholesterol ($P < 0.0001$), TGL ($P < 0.0001$), LDL-C ($P < 0.0001$), VLDL-C ($P < 0.0001$) and significantly substantially reduced HDL-C (P 0.0001) compared to the controls. [24]. In 2010, Fulghesu A et al studied obesity-related lipid profile and altered insulin incretion in adolescents with PCOS. They concluded that in the adolescent population studied, no differences were revealed in lipid profile between PCOS and controls. [25]

Insulin resistance and hyperinsulinemia are associated with decreased high - density lipoprotein (HDL) cholesterol and elevated triglyceride levels, and numerous studies have observed such abnormalities in women with PCOS. Anuradha kalra et al studied the correlation between insulin resistance and serum lipid profile in Indian women with PCOS in 2006. They concluded insulin resistance is associated with dyslipidemia in women with PCOS, independent of obesity. [26]

PCOS may set in early adolescent life, but clinically manifest in the reproductive age with long-term implications of diabetes, hypertension, hyperlipidaemia and cardiovascular disease; this cluster of disorders is known as 'X syndrome'. [27] . Bernies et al in their study found that compared with controls, patients with PCOS had higher plasma concentrations of triglycerides and lower high density cholesterol concentrations but did not find any significant differences in LDL cholesterol and total cholesterol concentrations. [28]

Keeping these facts in mind and realising the need for more data relating serum dyslipidemia, serum testosterone and obesity in women with PCOS of reproductive age group, we have conducted our study in a tertiary care Hospital in North-east India with the following objectives-

1. To assess the relation between body mass index and serum lipid profile in women with PCOS.
2. To assess the relation between body mass index and serum testosterone in PCOS women.
3. To correlate body mass index, serum lipid profile and serum testosterone in women with PCOS.

MATERIALS AND METHODS:

This is a population based cross-sectional study. It was carried out in 100 consecutive women diagnosed as having Polycystic Ovarian Syndrome in the reproductive age group (15-44 years). The institutional ethical committee approved the study protocol. Informed consent was obtained from all the participants.

A sample size of 100 was calculated by using the following formula:

$n = \{Z_{(1-\alpha/2)}\, Z_{(1-\beta)}\, .(\sigma)^2\} \div \Delta^2$,

where, $Z_{(1-\alpha/2)}$ is the confidence interval at 95%,

$Z_{(1-\beta)}$ is the power of test at 80%,

$(\sigma)^2$ is the standard deviation,

Δ^2 is the square of mean difference.

The diagnostic criteria are the Rotterdam ESHRE/ASRM PCOS group's revised 2003criteria. The study population was selected after taking a detailed history and observing the inclusion and exclusion criteria that included diseases likely to affect the lipid profile and serum testosterone level e.g., diabetes, hypertension and hypo- or hypergonadotropic disorders.

Inclusion criteria:

a) Diagnosed patients with PCOS in the reproductive age group (15-44yrs) fulfilling the Rotterdam criteria attending the OPD in department of Obstetrics and Gynaecology of the tertiary care hospital of Guwahati, Assam
b) Subjects with no history of drugs affecting hormonal and lipid metabolism.
c) Subjects who are willing to participate.

Exclusion criteria:

a) Patients with diabetes, hypertension, renal and liver failure and other endocrine disorder which alter the lipid profile or serum hormonal level of testosterone such as Cushing's syndrome, testosterone secreting tumour etc.
b) Exclusion of other androgen excess disorders
c) Patients receiving hormonal / non-hormonal treatment for PCOS or for any other causes.

Methodology: A pre-structured and pretested proforma was used to collect the data. Baseline data including age, height, weight, BMI, detailed medical history, clinical examinations and relevant investigations were included as part of the methodology.

Height: Height was measured using a portable vertical rod marked with a metric measurement scale.

Weight: Weight was measured using Libra flat, model 770 (machine no. -53084) weighing machine.

Body Mass Index (BMI): BMI is defined by weight in kilograms divided by height in metres squared (kg/m^2) was calculated for the subjects after the height and weight measurement.

Accordingly, the subjects in the study were divided into two groups [29]: -

A) Lean PCOS: - with BMI <23 kg/m^2
B) Obese or overweight PCOS: - with BMI ≥ 23kg/m

Collection of specimens: Under all aseptic and antiseptic precautions, 3 cc of blood was collected from each subject after 12 hours of fasting. The blood was then transferred into a vial and kept for 30 – 45 minutes in the stoppered vial and allowed to clot. The serum obtained was collected in a centrifuge tube and centrifuged for five minutes at 3000 rpm. The supernatant serum was then transferred to a sterile vial with the help of a pipette and used for estimation of serum total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-c), high density lipoprotein-cholesterol (HDL-c) and serum testosterone. When the serum was not used immediately it was stored at 2 – 8 degrees centigrade for a maximum of five days.

The biochemical estimation of the lipid profile was done using digital Photocolorimeter and the

estimation of serum testosterone was done in MINIVIDAS machine.
In our study the criteria adopted was in consonance with NCEP-ATP III guidelines. Deranged lipid profile was considered if any of the cholesterol, triglycerides and HDL cholesterol were deranged and the individual cut-offs taken were as [30]: -
Cholesterol ≥ 200mg/dl
Triglycerides ≥ 150mg/dl
HDL- cholesterol <50mg/dl
LDL cholesterol ≥ 130mg/dl

Serum Testosterone: It is being measured as an automated quantitative test by the use of the instrument of the VIDAS family using the Enzyme Linked Fluorescent Assay (ELFA) technique.
Principle: - The assay principle combines an enzyme immunoassay competition method with a final fluorescent detection.
Reference Range: -
Female – 0.1-0.9 ng/ml.

Data management and statistical analysis: The completed proforma was regularly checked for accuracy and consistency. After entering the data into the Microsoft Excel programme, the required analysis and calculation were carried out. Data is presented as mean ± standard deviation. P value of< 0.05 and < 0.01 is considered statistically significant.

RESULT AND DISCUSSION:
In the present work, 100 women samples diagnosed as having Polycystic Ovarian Syndrome (PCOS) in the reproductive age group (15-44 years). Out of the 100 women, 59 were obese and the rest 41 were lean PCOS. The sample has been studied for serum lipid profile and serum testosterone in relation to their BMI.
The following are the important results and observations found during the course of the study-

Comparison between different parameters of lean and obese PCOS group:
In the study we are interested to test whether there are significant differences between all the parameters among the two groups i.e., the lean and obese PCOS women. For this purpose, unpaired Student's t-test has been applied. Significance was set at $p < 0.01$ and $p < 0.05$. All statistical analyses were performed by using Graph Pad InStat. The results are analysed in the **Table 1, Table 2, Table 3, Table 4 and Table 5.**

Table 1: Table showing the comparison of the parameter **BMI (kg/m^2)** among the Lean and Obese PCOS women.

Group	Mean	SD	degrees of freedom	t-value	Significance	Conclusion
Lean PCOS (N=41)	21.13	1.21	98	15.296**	p<0.01	It has been found that there is a highly significant difference in BMI level between the Lean and Obese PCOS women at 0.01 level of significance (p<0.01).
Obese PCOS(N=59)	26.65	2.08				

**→Highly significant.
(The critical value of 't' with 41+59-2=98 at 0.01 level of significance is 2.63; at 0.05 level of significance is 1.98.)

Table 2: Table showing the comparison of the different parameters **HDL (mg/dl)** and **Triglyceride [TG] (mg/dl)** among the Lean and Obese PCOS women.

Comparison of the parameter	Group	Mean	SD	d.f.	t-value	Significance	Conclusion
HDL (mg/dl)	Lean PCOS (N=41)	57.78	10.48	98	2.576 *	p<0.05	The obese PCOS category of women has lower mean score of the parameter HDL than their lean PCOS counterparts which has been found to be statistically significant with p<0.05.
	Obese PCOS(N=59)	52.29	10.49				
Triglyceride [TG] (mg/dl)	Lean PCOS (N=41)	127.98	19.47	98	3.461* *	p<0.01	It has been found that there was a highly significant difference in TG level between the Lean and Obese PCOS
	Obese PCOS(N=59)	143.59	23.89				

							women at 0.01 level of significance (p<0.01).

HDL: *→Significant, Triglyceride [TG] (mg/dl): **→Highly Significant, d.f.-degrees of freedom

Table 3: Table showing the comparison of the parameter **LDL (mg/dl)** and **Total Cholesterol (mg/dl)** among the Lean and Obese PCOS women.

Comparison of the parameter	Group	Mean	SD	d.f.	t-value	Significance	Conclusion
LDL (mg/dl)	Lean PCOS (N=41)	65.78	29.35	98	0.689 (N.S.)	p>0.05	The difference is not statistically significant as p>0.05. Hence, the difference is negligible.
	Obese PCOS (N=59)	69.97	30.22				
Total Cholesterol (mg/dl)	Lean PCOS (N=41)	149.15	25.32	98	0.433 (N.S.)	p>0.05	Total Cholesterol (mg/dl) among the obese PCOS women is a little bit higher than that of the lean PCOS women, but the 't'-value shows that the difference was not significant as p>0.05.
	Obese PCOS (N=59)	151.42	26.28				

N.S.→ Not Significant, d.f.-degrees of freedom

Table 4: Table showing the comparison of the parameter Serum **Testosterone (ng/ml)** among the Lean and Obese PCOS women.

Group	Mean	SD	degrees of freedom	t-value	Significance	Conclusion
Lean PCOS (N=41)	1.44	0.543	98	1.79	p>0.05	In the parameter Testosterone (ng/ml), the mean scores of both the groups are found to be slightly higher than the normal value, which is 0.9 ng/ml. Again, it was found higher among the obese PCOS women than their lean PCOS counterparts but, the difference is statistically not significant (p>0.05).
Obese PCOS(N=59)	1.62	0.47				

Table 5: Table showing the correlation coefficient (r) between the BMI and all the parameters among the entire sample PCOS women (N=100).

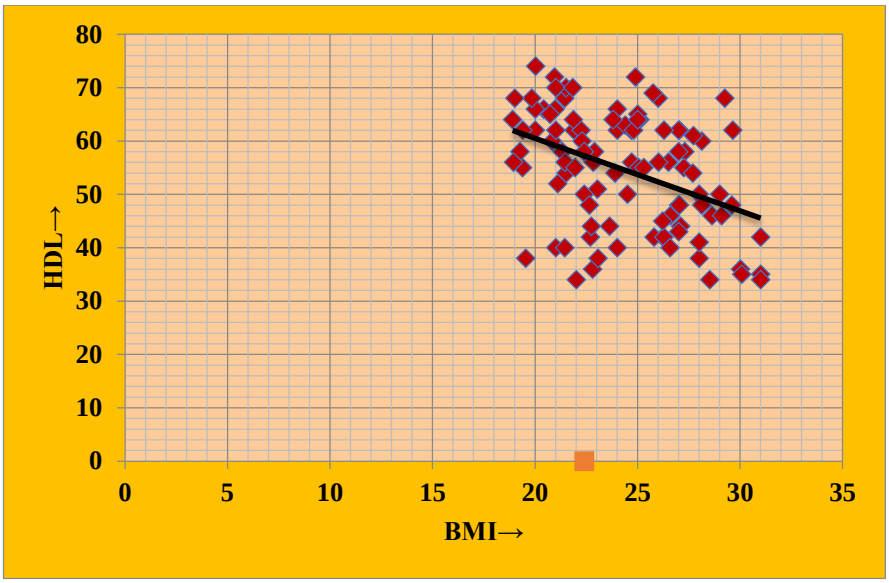
Parameter	R
HDL	-0.41
Triglyceride	0.51
LDL	0.24
Cholesterol	0.19
Serum Testosterone	0.09

Correlation between bmi and all the parameters among the entire PCOS women (n=100):

To correlate Body Mass Index with the parameters HDL, Triglyceride, LDL, Cholesterol and Serum Testosterone among the entire sample women, Pearson's correlation coefficient (r) has been applied. The range of the correlation coefficient is ±1. i.e. $-1 \leq r \leq +1$. Following table shows the coefficient of correlation (r) between the BMI and all the parameters. **[Table 5]**

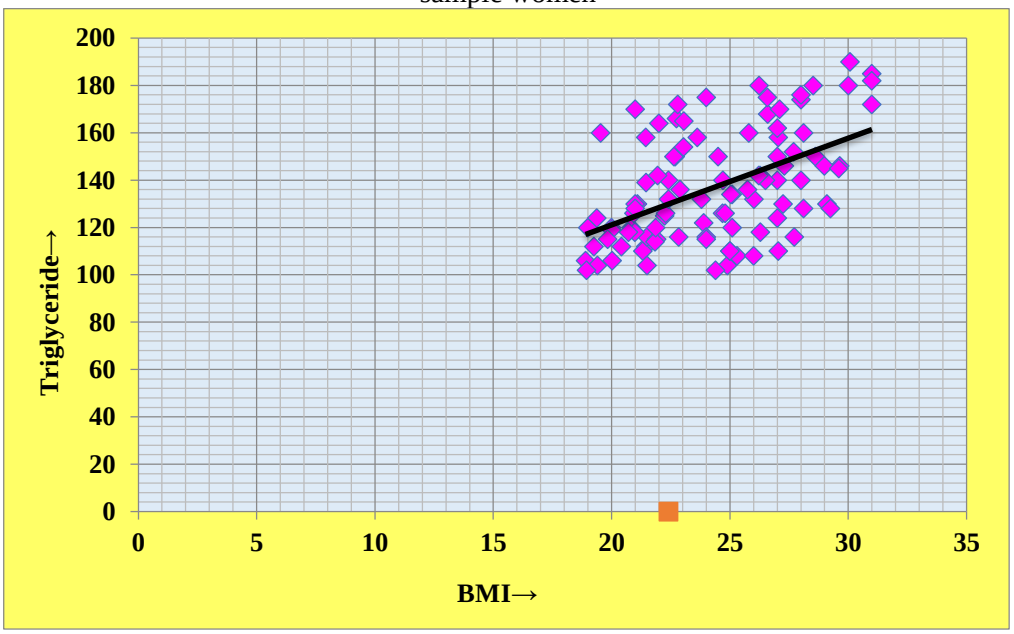
The calculated value of the correlation coefficient 'r' between BMI and HDL score has been found as -0.41. Hence, it can be commented that there is a negative correlation between the parameter BMI and HDL. **[Fig 1]**

Figure 1: Scatter diagram showing the correlation between BMI and HDL level among the entire sample women



The correlation coefficient 'r' has been found as 0.51 between BMI and the Triglyceride among the entire PCOS women which shows a positive linear relationship between the two variables. **[Fig 2]**

Figure 2: Scatter diagram showing the correlation between BMI and Triglyceride level among the entire sample women



The correlation coefficient 'r' between the two parameters BMI and LDL among the entire PCOS women is calculated as 0.24 as depicted in **Table 5**. The scatter diagram in figure 3 has depicted a moderate positive trend between the two variables. So, it can be concluded that there is a moderately positive correlation between BMI and LDL levels of the PCOS women. **[Fig 3]**

Figure 3: Scatter diagram showing the correlation between BMI and LDL level among the entire sample women

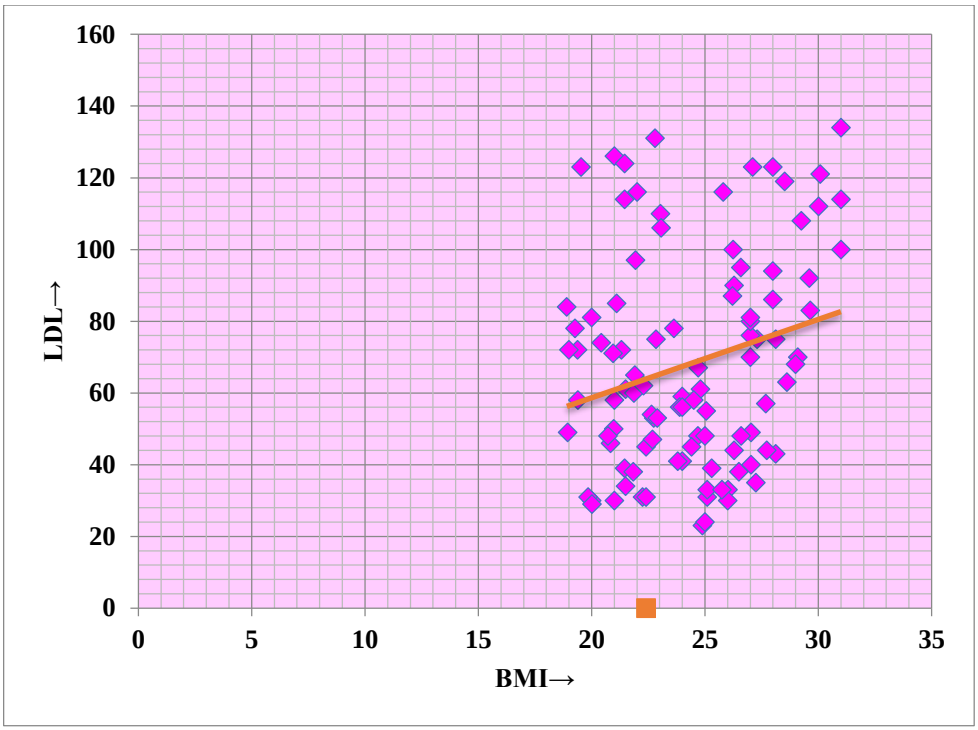
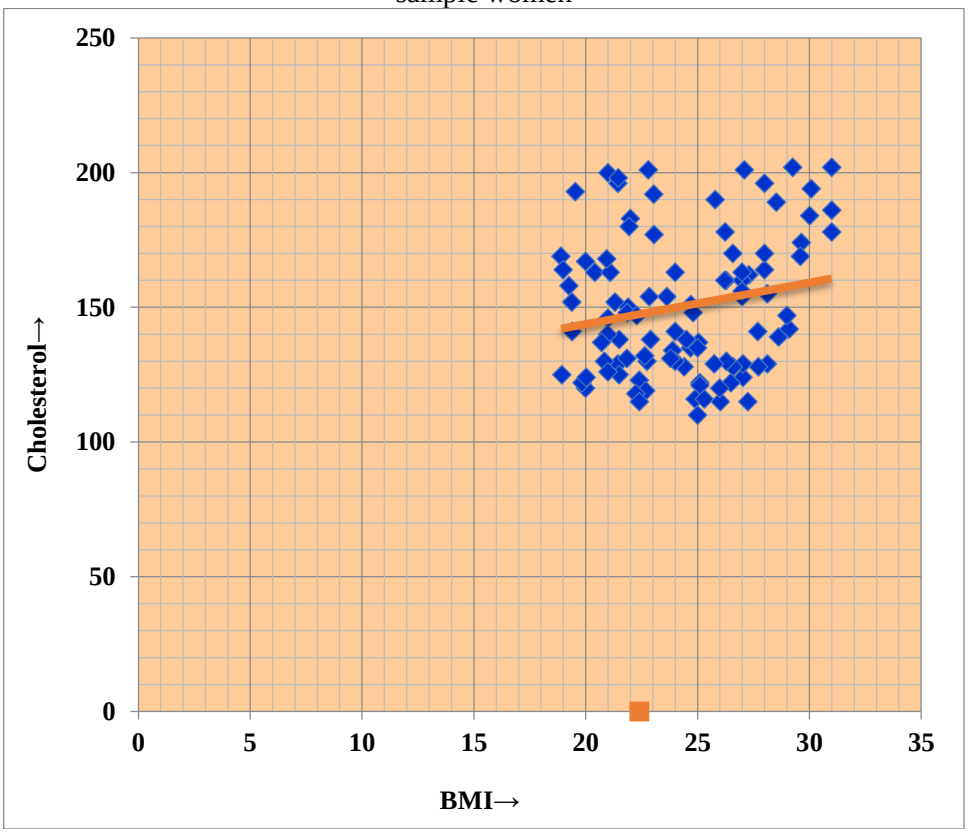


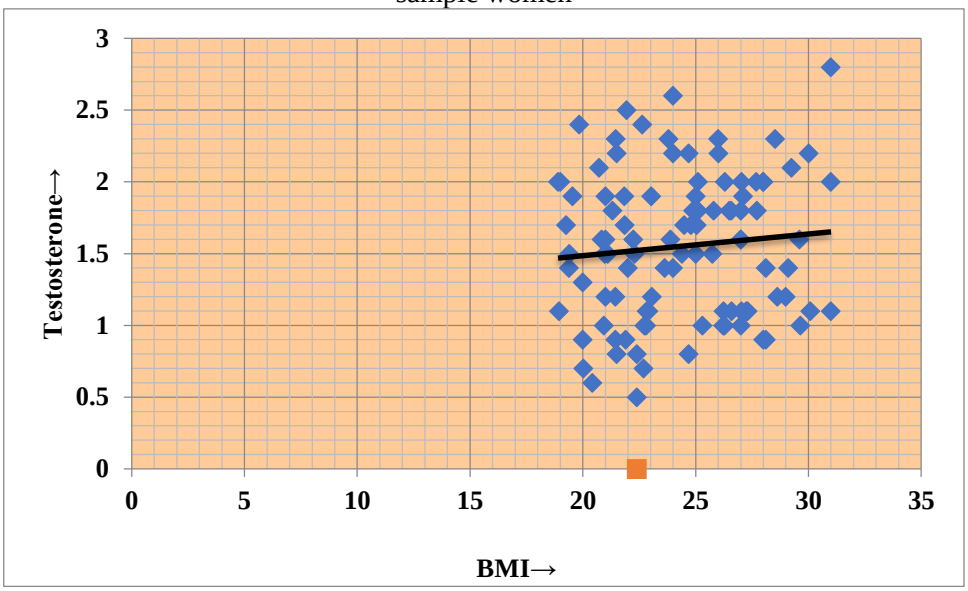
Table 5 and **figure 4** have depicted the relationship between the parameters BMI and Cholesterol level among the entire sample women. The coefficient of correlation 'r' is found to be 0.19, which indicates a low positive correlation. **[Fig 4]**

Figure 4: Scatter diagram showing the correlation between BMI and Cholesterol level among the entire sample women



The correlation coefficient 'r' between the two parameters BMI and Testosterone among the entire PCOS women is calculated as 0.096 as shown in **Table 5**. The scatter diagram in figure 5 also shows a negligible or too slight relationship between the two variables. **[Fig 5]**

Figure 5: Scatter diagram showing the correlation between BMI and Testosterone level among the entire sample women



Insulin resistance appears to be a crucial flaw that accounts for the majority of the endocrine abnormalities seen in PCOS within the framework of a coherent theory. Insulin resistance is associated with abnormal responses of the ovarian follicle to FSH, which lead to anovulation and androgen secretion. This results in noncyclic formation of estrogen from androgens in peripheral tissues. Estradiol causes aberrant gonadotropin release along with increased androgen and insulin levels. This induces an anovulatory state that encourages the continual production of LH, testosterone, oestrogen, and steroid precursors. In adipose tissue, insulin resistance results in increased hydrolysis of stored triglycerides and elevated circulating free fatty acid levels.

Obesity has recently been identified as a key predictor of the development of metabolic syndrome in PCOS participants. Since insulin resistance is associated with dyslipidemia and MBS in women with PCOS, screening these women for insulin resistance is recommended. Given that PCOS is a systemic metabolic illness, it is no longer viable to see it as a solely gynecologic issue.

Pikee Saxena et al investigated in PCOS woman about the clinical, hormonal, and metabolic assessment in relation to body mass index in 2012. The lipid profile was found to be deranged in both the lean and obese PCOS group- 14.2% vs. 31% respectively. In the study, it was found that serum HDL-c level is decreased significantly in the obese PCOS group then the lean group. Also, the serum triglyceride level was significantly more in the obese group as compared to the lean group. [31]

Moini et al in the year 2012, studied 282 women with PCOS to determine the prevalence of metabolic syndrome in the study group. They found that insulin resistance and hyperinsulinemia are considered to be key pathogenic factors in the development of the components of metabolic syndrome such as abnormal glucose tolerance, dyslipidemia and hypertension. Their study indicated that women with PCOS have a high prevalence of metabolic syndrome and its individual components, particularly decreased high density lipoprotein levels. [32]

In recent years, increasing focus is on the non-reproductive aspects of PCOS. The long-term impact of the above-mentioned disturbances and its association with the overall impact on the health has brought in considerable interest on follow-up studies and intervention studies.

CONCLUSION:

From the findings it can be concluded that HDL-c parameter of the lipid profile decreased with increasing BMI. Also, Triglyceride level increased with the increased BMI. Moreover, a moderately positive correlation is seen between the BMI and LDL-c and total cholesterol parameter though the difference in the values between the lean and obese PCOS is not statistically significant. However, the serum testosterone level is increased in the sample

population more than the normal range irrespective of the BMI.

The above said alterations confirm that Polycystic Ovarian Syndrome(PCOS) contributes to the development of an atherogenic lipid profile with the patient at a higher risk of cardiovascular disease and metabolic syndrome. Also, it confirms the association of hyperandrogenism with PCOS independent of BMI of the patient.

However further studies with a greater number of the representative sample is required to establish the association of dyslipidemia, serum testosterone and body mass index and thereby generalise the conclusion of the present study. Data on insulin levels are needed for greater understanding of the pathophysiology and manifestation of PCOS and to study the relation between insulin resistance and dyslipidemia. Also, due consideration has to be given to the association of physical activity, parity and familial linkage with the PCOS.

Conflict of interest

None.

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