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Relationship between Serum Homocysteine and Insulin Resistance in Women with Polycystic Ovary Syndrome: A Cross Sectional Study at a Tertiary Care Hospital in Dhaka, Bangladesh

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Abstract:
Background: *Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in infertile women characterized by both reproductive and metabolic dysfunctions of varying degrees. A possible association of serum homocysteine (Hcy) with insulin resistance in women with PCOS may be helpful to utilize these parameters for better management of PCOS and for the early diagnosis of subclinical inflammation and atherosclerosis in the asymptomatic individual. Aim of this study is to evaluate the association of serum homocysteine (Hcy) with insulin resistance in women with PCOS.*
Materials and Methods*: This cross-sectional study was conducted in the Department of Biochemistry and Molecular Biology, BSMMU. After IRB approval, data were collected from 108 study subjects (60 PCOS with insulin resistance and 48 PCOS without insulin resistance) attending the OPD of Obstetrics and Gynecology, department of Reproductive endocrinology and Infertility, department of Endocrinology and Metabolism, BSMMU. Blood samples were collected from each individual to estimate serum homocysteine, fasting insulin and fasting plasma glucose.*
Results*: Age and family history were identical in both groups. But increased BMI was predominent in PCOS with insulin resistance group than PCOS without insulin resistance (p=0.001). Homocysteine was significantly raised in PCOS with insulin resistance group and correlated with insulin resistance index (rho =+0.408, p=0.001), serum insulin (rho=+0.352, P=0.006) and BMI (rho=+0.260, P=0.045). Homocysteine was not correlated with fasting plasma glucose. Serum homocysteine shows a higher risk for developing insulin resistance in PCOS patients (Odd ratio=infinity).*
Conclusion: *Serum homocysteine levels are elevated in PCOS women with insulin resistance and are associated with the insulin resistance index, serum insulin and BMI. The intense treatment of hyperhomocysteinemia in women with PCOS might improve reproductive outcome and contribute to protect from cardiovascular risks.*
Key Word*: Polycystic ovary syndrome, Homocysteine, Insulin resistance, Cardiovascular diseases.*

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I. Introduction

An endocrine disorder known as polycystic ovarian syndrome (PCOS) affects 3–10% of women who are of childbearing age[1, 2, 3]. Its distinguishing features include hirsutism, alopecia, and acne, as well as chronic anovulation and clinical hyperandrogenism symptoms. PCOS is commonly diagnosed using the Rotterdam criteria (2003), which call for the presence of at least two or three characteristics. Clinical or biochemical hyperandrogenism, persistent disruption of the menstrual cycle, and polycystic ovaries—defined as having more than 10 follicles and 10 ml of ovarian volume—are among the Rotterdam criteria for PCOS[4]. In this study, PCOS is diagnosed using the international evidence-based guideline for the diagnostic and therapy of polycystic ovarian syndrome, 2018. According to this recommendation, PCOS can be diagnosed by ultrasonography, clinical or biochemical hyperandrogenism, and menstrual history.

Type 2 diabetes, gestational diabetes mellitus (DM), glucose intolerance, and irregularities in insulin synthesis and activity are among the conditions that women with PCOS are more likely to experience[5]. Moreover, patients with type 2 diabetes and 30 to 40 percent of women with PCOS exhibit a similar decline in

insulin sensitivity[6].
Our bodies produce homocysteine (Hcy), a nonessential amino acid, from methionine, another amino acid produced during the metabolism of proteins and absent from the typical diet. Deficits in vitamin B12 and folate, as well as genetic abnormalities in enzymes involved in homocysteine metabolism, like methylene tetrahydrofolate reductase (MTHFR), are the causes of hyperhomocytenemia.

Furthermore, it may be associated with some long-term medical conditions and drugs such as fibrates and nicotinic acid[7,8].Numerous investigations have looked at the relationship between insulin resistance (IR) and plasma homocysteine levels in a particular group of PCOS patients. Increased homocysteine levels in plasma can result from compensatory hyperinsulinemia brought on by hyperhomocystenemia, which can also affect the action of the enzymes cystathionine beta-synthase (CBS) and methylene tetrahydrofolate reductase (MTHFR)[7]. Because insulin suppresses the function of the liver's cystathionine beta-synthase, it has been shown that insulin levels also modulate homocysteine levels[9]. It has been observed that insulin resistance, body mass index, and homocysteine levels are significantly correlated[10].

Atherosclerotic vascular disease, cerebrovascular accidents, and recurrent venous/arterial thromboembolism are all independently correlated with hyperhomocysteinemia.8 Similar pathogenic pathways in the peripheral arteriolar and capillary beds have been postulated to give rise to insulin resistance, along with endothelial dysfunction in skeletal muscle, liver, adipose tissue, and kidney[11].While anovulatory infertility is the most common symptom of PCOS in women, the condition is also linked to long-term negative consequences like metabolic syndrome and cardiovascular disease. It has been demonstrated that women with PCOS have higher levels of many indicators of increased metabolic activity, such as serum homocysteine, which calls for more research to address the long-term negative health implications in these women.

From this point of view, this study was aimed to evaluate the levels of homocysteine which is associated with endothelial inflammation and to evaluate it's relationship with insulin resistance in women with PCOS.

II. Material And Methods

Study design: Cross-Sectional Study.
Place of study: Department of Biochemistry & Molecular Biology, BSMMU.
Study duration: One year (March 2022 – February 2023).
Study population: PCOS patients (diagnosed by international evidence-based guideline for the assessment and management of polycystic ovary syndrome, 2018) attending at departments of Obstetrics and Gynecology, department of Reproductive endocrinology and Infertility, department of Endocrinology and Metabolism BSMMU.
Sample size: 108
Sample size calculation: Total of 108 study subjects (60 patients in PCOS with insulin resistance group and 48 patients in PCOS without insulin resistance group) were enrolled using following formula,

n=$(Z\alpha + Z\beta)^2 x$ ($\sigma_1 2 + \sigma_2 2$)/($\mu 1 - \mu 2$)2 (DeUgarte et al., 2005)

Subject selection:

Group1: PCOS patients with insulin resistance.
Group2: PCOS patients without insulin resistance.
Sampling method: Non-random purposive sampling.
Inclusion criteria:
1.Diagnosed polycystic ovary syndrome patients. (Diagnosed by international evidence-based guideline for the assessment and management of polycystic ovary syndrome, 2018).
2.Age of women (18-35) years.
3.All eligible women giving informed written consent.

Exclusion criteria:
1.Patients with renal, thyroid and hepatic dysfunction, having androgen producing tumor, cardiovascular diseases, type 1 or 2 diabetes, Psoriasis, Eczema, Rheumatoid arthritis, Malignancy, Pregnancy, taking hormonal supplementation or insulin sensitizers- folic acid- vit B12- phenytoin- carbamazepine- methotrexate and NASID, History of cigarette smoking, alcohol consumption.

Procedure methodology

After written informed consent was obtained, A pretested data collection sheet formatted first in English then translated in Bangla was used as a data collection tool. The sheet included three sections. Section A contained different information about socio-demographic characteristics such as age and occupation. Section B contained information related to PCOS and section C included test reports.

With all aseptic precautions, blood sample was drawn from the study subjects by a trained phlebotomist of one-point sample collection center, BSMMU following overnight fasting (10-12 hours). Blood sample (5 ml) was collected from the anti- cubital vein using a disposable plastic syringe. At first, 3ml blood sample was collected in a plain test tube (no anti-coagulant) for estimation of serum homocysteine, and serum insulin. Then 2 ml blood was collected in a test tube containing Na-fluoride for estimation of fasting plasma glucose. Then all test tubes were centrifuged at 3000rpm for 10 minutes to get the serum & plasma for laboratory tests as soon as possible. Ensuring adequate quality control measures, the entire biochemical tests were carried out in the Department of Biochemistry and Molecular Biology, BSMMU, Dhaka.

Laboratory methods:

• Estimation of serum homocysteine by chemiluminescence method.
• Estimation of fasting plasma glucose by GOD-PAP method.
• Estimation of serum insulin by chemiluminescence method

Statistical analysis

All the data were compiled, tabulated and analyzed statistically using a personal computer and Statistical Package for Social Science (SPSS) version 26.0. In normal distribution, continuous data were expressed as mean (+SD) or as median (inter- quartile range) in case of skewed distribution. Normally distributed quantitative data were analyzed by Unpaired t-test. In case of data with skewed distribution Mann-Whitney U-test was applied. Spearman's rank correlation coefficient test was done to show the association between serum homocysteine with insulin resistance. Odd ratio was used to determine the risk of developing insulin resistance due to hyperhomocysteinemia. P-value < 0.05 was considered statistically significant.

III. Result

This cross-sectional study was carried out in the Department of Biochemistry and Molecular Biology, BSMMU to evaluate the relationship of serum homocysteine with insulin resistance in women with PCOS. One hundred eight (108) PCOS patients (60 PCOS with insulin resistance and 48 PCOS without insulin resistance) were enrolled in the study from the department of Obstetrics and Gynecology, department of Reproductive endocrinology and Infertility, department of Endocrinology and Metabolism BSMMU. Blood sample was collected with full aseptic precaution for estimation of FPG, fasting insulin, and serum homocysteine . Insulin resistance index was calculated by the following formula:

HOMA-IR= Glucose X insulin/22.5

Appropriate statistical techniques were applied for data analysis. P-value < 0.05 was considered statistically significant. Results are presented in appropriate tables and graps in the following pages.

Table no 1: Comparison of age between PCOS patients with insulin resistance and PCOS patients without insulin resistance(n=108)

Variable	**PCOS with insulin resistance (n=60)** Mean ±SD	**PCOS without insulin resistance (n=48)** Mean ±SD	***p*-value**
Age group (in years) (18-35) years	25.27±4.99	24.42±5.0	0.382

Unpaired t-test was applied to see the level of significance

Table no 1 shows there was no stastistically significant differences between PCOS patients with insulin resistance and PCOS patients without insulin resistance in term of age. All the PCOS patients were statistically identical in respect of age.

Table no 2: Distribution of study subjects by anthropometric measurement and clinical parameters (n=108).

Variables	PCOS with insulin resistance (n=60)	PCOS without insulin resistance (n=48)	*p*-value
BMI (kg/m2)	27.35±2.71	24.00±1.52	0.001
Systolic blood pressure	117.50±10.83	109.79±12.16	0.001
Diastolic blood pressure	69.50±6.75	66.67±7.17	0.037

Unpaired t-test was applied to see the level of significance.

Table no 2 shows BMI was significantly high in PCOS patients with insulin resistance than PCOS patients without insulin resistance (P=.001). There was also significant difference in term of systolic blood pressure and diastolic blood pressure between the groups.

Table no 3: Biochemical parameter of the study subjects (n=108).

Parameter	PCOS with insulin resistance (n=60)	PCOS without insulin resistance (n=48)	*p*-value
Homocysteine Median (IQR)	11.52(9.49-14.11)	6.25(5.16-8.30)	<0.001*

Mann-Whitney U test was applied to see the level of significance

Table no 3 shows serum homocysteine was significantly high in PCOS patients with insulin resistance than PCOS patients without insulin resistance and the p value was <0.001.

Table no 4: Correlation of homocysteine with fasting plasma glucose, fasting Insulin, insulin resistance index, BMI and CRP in PCOS patients with insulin resistance (n=60)

Parameters		PCOS with insulin resistance (n=60)	
		rho value	*p*-value
Serum homocysteine	Fasting plasma glucose	-0.078	0.552
	Fasting Insulin	**0.352****	**0.006**
	Insulin resistance Index	**0.408****	**0.001**
	BMI	**0.260**	**0.045**

spearman's rank correlation-coefficient test was done

Table no 4 shows in PCOS patients with insulin resistance serum homocysteine was strongly correlated with insulin resistance index. Again, a moderate correlation was found between serum homocysteine and fasting insulin. A weak correlation was found between serum homocysteine and BMI.

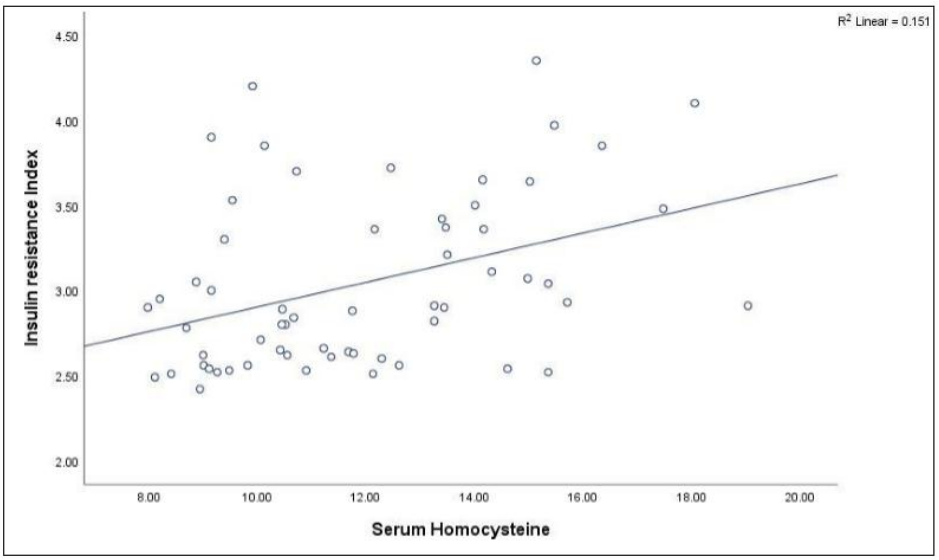

Figure no 1: Correlation of serum homocysteine with insulin resistance index in PCOS patients with insulin resistance.

Figure no 1 shows that serum homocysteine had significant positive correlation with insulin resistance index (rho =+0.408, P=0.001).

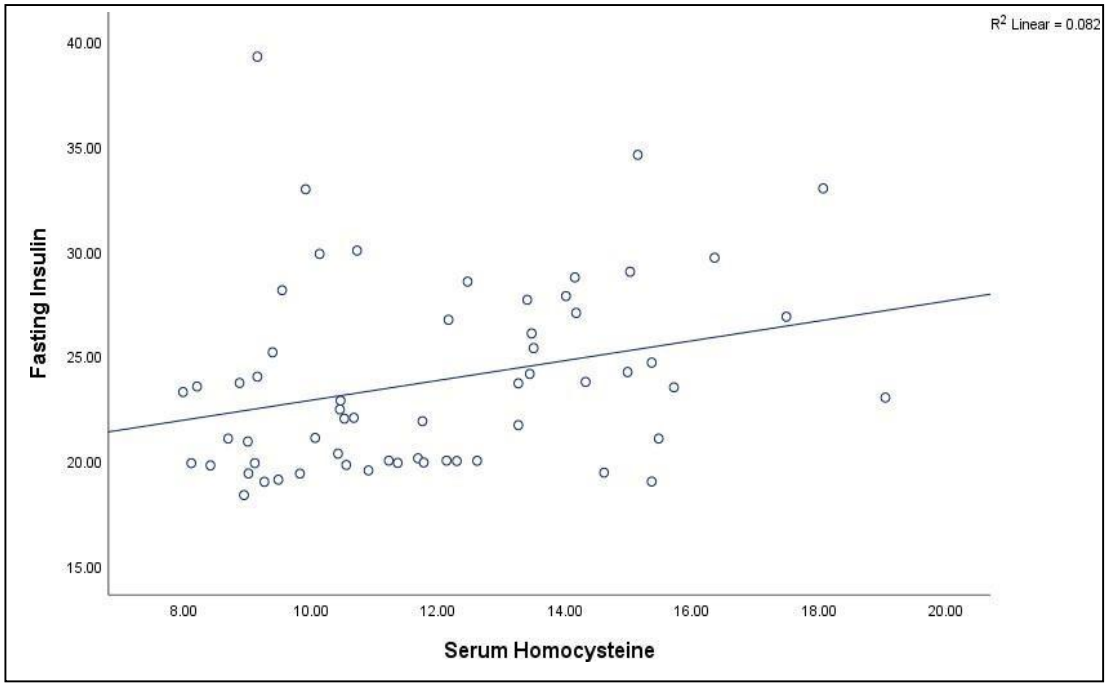

Figure no 2: Correlation of serum homocysteine with fasting insulin in PCOS patients with insulin resistance.

Figure no 2 shows that serum homocysteine had significant positive correlation with fasting insulin (rho =+0.352, P=0.006).

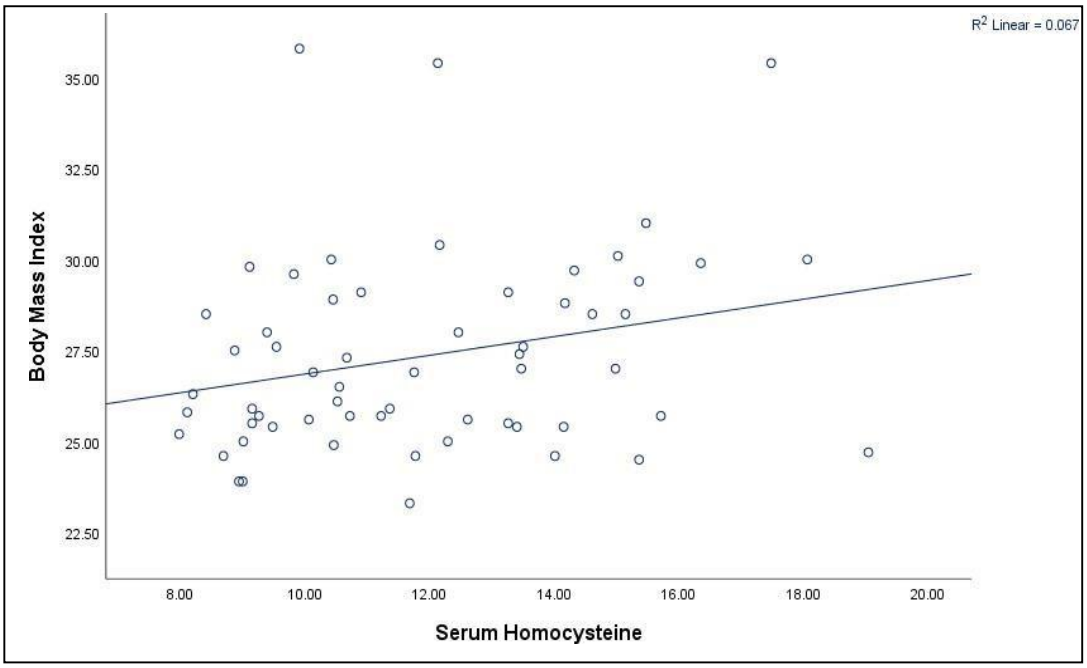

Figure no 3: Correlation of serum homocysteine with BMI in PCOS patients with insulin resistance.

Figure no 3 shows that serum homocysteine had significant positive correlation with BMI (rho =+.260, P=0.045).

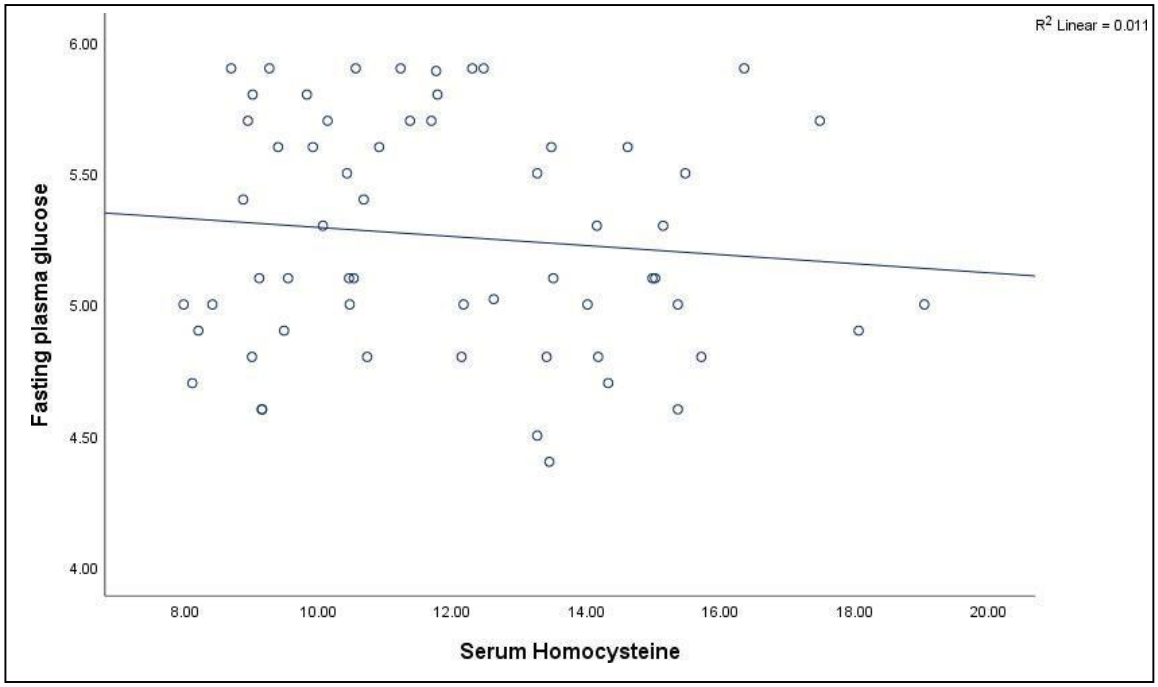

Figure no 4: Correlation of serum homocysteine with fasting plasma glucose in PCOS patients with insulin resistance.

Figure no 4 shows that serum homocysteine had no correlation with fasting plasma glucose (rho =-0.078, P=0.552).

Table no 5: Odd ratio of homocysteine for insulin resistance(n=108)

Homocysteine	PCOS with insulin resistance (n=60)	PCOS without insulin resistance (n=48)	Odd ratio
> 15 µmol/L	10	0	**>1(infinity)**
≤15 µmol/L	50	48	

Table no 5 shows the odds ratio of homocysteine for insulin resistance. Here serum homocysteine showed a higher risk for insulin resistance in PCOS patients (odd ratio infinity).

IV. Discussion

Recently, research has focused on systemic and local effects of IR and homocysteine and their secondary effects on reproductive system. Homocysteine levels are positively correlated to risk of cardiovascular disease and complications, by increasing oxidative stress in vascular endothelium, activation of platelets13,14 and impairment of blood flow15 .There are a number of studies that have investigated the mean homocysteine, fasting insulin and glucose levels in women with PCOS but the relationship between hyperhomocysteinemia and IR in PCOS patients still remain controversial. In this study, most of the confounding variables were excluded during enrollment of participants and others during analysis. The prevalence of IR in PCOS patients ranges from 44 to 70%. This wide range may be due to several factors, including the heterogeneity of the diagnostic criteria for PCOS employed in these studies. 16

In this present study, it was found that in total 108 patients, 60 (55.55%) PCOS patients were with insulin resistance and 48 (44.44%) PCOS patients were without insulin resistance. The mean age of PCOS patients with insulin resistance was (25.27±4.99 years) and in PCOS without insulin resistance was (24.42±5.0 years). The difference was not statistically significant (P>0.05). In this study, the BMI in PCOS with insulin resistance was (27.35±2.71kg/m2) and in PCOS without insulin resistance was (24.00±1.52 kg/m2) which was statistically significant (P=0.001).

Similarly, Nervana et al., (2012) observed that the mean age in PCOS with insulin resistance was (29 ± 5 years) and PCOS without insulin resistance (28 ± 6 years) which was not statistically significant between the groups.17 In this study they also found that the mean BMI in PCOS patients with insulin resistance was (30.2 ± 1.11 kg/m2) and the in PCOS patients without insulin resistance was (26.3± 1.09. kg/m2). There was statistically significant difference regarding BMI between the groups (P< 0.001). Rekha et al., (2012) conducted

a study and showed BMI of PCOS patients with insulin resistance was significantly high (29.91±2.32 kg/m2) than in PCOS patients without insulin resistance is (27.09±1.78 kg/m2); P<0.001.18

In this study, serum homocysteine levels were significantly high in PCOS patients with insulin resistance than PCOS women without insulin resistance which was 11.52(9.49-

14.11) µmol/L and 6.25(5.16-8.30) µmol/L respectively(P<0.001). High serum homocysteine was significantly correlated with BMI (r=+0.260 and P=0.045). These results were in agreement with a study done by Guzelmeric et al., (2007) who concluded a significant interaction between increasing homocysteine and BMI (r=0.349).19 Nervana et al., (2012) also found that serum homocysteine levels were highly correlated with BMI (r=0.521 and P < 0.001).17

In this study, it was observed that homocysteine was strongly correlated with insulin resistance (r=+0.408, P=0.001). Rekha et al., (2012) concluded, a positive correlation of total homocysteine levels with insulin (r=0.584) and HOMA-IR (r=0.595), which was also statistically significant (P<0.001). A study conducted by Yilmaz et al., (2008) reported correlation between the mean homocysteine and the fasting insulin levels and also between the serum Hcy concentrations, glucose/insulin ratios and HOMA IR values in the PCOS patients with IR (P = 0.027, P = 0.012, P = 0.01)10,18. The homocysteine levels were unrelated to serum glucose concentrations in the PCOS patients with IR (P > 0.05). They also conclude that in polycystic ovary syndrome the elevated homocysteine was associated with the serum insulin level rather than androgen excess. Bayraktar et al, (2004) confirmed the association between IR (determined by HOMA) and hyperhomocysteinemia and proved that homocysteine levels were higher in PCOS patients with IR.20

In this study, it was observed that serum homocysteine concentration was correlated with serum fasting insulin not related to plasma glucose. Odd ratio of homocysteine for insulin resistance was infinity that means homocysteine showed a higher risk for developing insulin resistance in PCOS patients. Similarly, Atanasova Boshku et al., (2017) did a study and observed no significant correlation between serum homocysteine and plasma glucose.21

Hyperhomocysteinimia inhibites adipose tissue insulin sensitivity by inducing endoplasmic reticulum stress, promoting proinflammatory cytokine production and facilitating macrophage infiltration.22 Proinflammatory M1 macrophages inhibit insulin sensitivity by producing cytokines, whereas anti-inflammatory M2 macrophages have the opposite effect23 . Homocysteine levels is influenced by a number of variables such as smoking, renal function, vitamin B status and enzyme dysfunction states. History of smoking was taken and those who have history of smoking were excluded from this study. Although renal status was not examined, all of these women enrolled in this study were in good general health and none had hypertension or oedema. Methyltetrahydrofolate reductase (MTHFR) enzyme deficiencies and vitamin levels were not screened in this patient group. Vitamin B12 levels and folic acid levels were examined in the study by Yarali et al., (2001) and observed no significant differences between PCOS and controls.24 As the frequency of this mutation is in the order of 5±10% in unselected populations, it seems unlikely that MTHFR status could be responsible for the differences between homocysteine in PCOS and controls in this study.

V. Conclusion

This study concludes that serum homocysteine was increased in PCOS patients with insulin resistance and was significantly associated with insulin resistance, serum insulin and BMI. Odd ratio of homocysteine for insulin resistance was infinity in PCOS women. By clarifying the relationship between insulin resistance and other biochemical parameters, may enlighten the better treatment options and avert women from short term and long-term risk factors such as cardiovascular disease, type 2 diabetes mellitus, infertility, and recurrent miscarriages.

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