

Correlation of Serum Homocysteine Levels and Hyperinsulinaemia with Body Mass Index in Polycystic Ovarian Syndrome

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting women in reproductive age group. The interrelationship of serum homocysteine, homeostatic assessment of insulin resistance (HOMA-IR) and body mass index amongst overweight, obese and non-obese PCOS patients is not fully established. **Aims:** We aimed to study the correlation of serum homocysteine levels and hyperinsulinaemia with body mass index (BMI) in PCOS patients. **Study Setting and Design:** This was a case-control study in which 35 women with PCOS and 35 non-PCOS women acting as controls were enrolled. **Materials and Methods:** Cases were identified by Rotterdam's criteria. (IR) indices, HOMA determination and serum homocysteine levels were determined and their correlation with BMI was studied. **Statistical Analysis Used:** Student's *t*-test and analysis of variance test were used for statistical analysis. The Pearson correlation coefficient was then used to estimate the correlation. **Results:** On overall evaluation, a significant positive correlation of fasting insulin, HOMA-IR and serum homocysteine) was observed ($P < 0.05$), however, on evaluating the correlation of these markers independently in cases and controls, only fasting insulin and HOMA-IR showed a significant correlation. In a multivariate model where PCOS was considered a dependent variable with age, fasting glucose, HOMA-IR, serum homocysteine and body mass index as the independent variables, only serum homocysteine levels were found to be significantly associated with the dependent variable (odds ratio = 1.172; 95% confidence interval = 1.032–1.330). **Conclusion:** PCOS women had significantly higher mean fasting glucose, fasting insulin, HOMA-IR and homocysteine levels as compared to non-PCOS controls. Mean HOMA-IR, homocysteine and fasting insulin levels showed a significant incremental trend with increasing BMI category in overall evaluation as well as in cases and controls independently.

KEYWORDS: *Body mass index, homocysteine, insulin resistance, polycystic ovary syndrome*

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting women in reproductive age group and is a significant cause of stress.^[1] It affects nearly 5%–10% of women of reproductive age. PCOS is characterised by oligo- or anovulation, clinical or biochemical hyperandrogenaemia

and/or polycystic ovaries on ultrasonography.^[2] It has been shown to be associated with type 2 diabetes mellitus, increased risk of cardiovascular disease^[3,4] and endometrial cancer.^[5] In view of the absence of an

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Received: 15-10-2021
Accepted: 28-02-2022

Revised: 27-02-2022
Published: 31-03-2022

Access this article online

Quick Response Code:



Website:
www.jhrsonline.org

DOI:
10.4103/jhrs.jhrs_147_21

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How to cite this article: Bhushan R, Sinha P. Correlation of serum homocysteine levels and hyperinsulinaemia with body mass index in polycystic ovarian syndrome. *J Hum Reprod Sci* 2022;15:34-41.

ideal explanatory model for pathogenesis of PCOS, a number of possible factors responsible for pathogenesis have been suggested. These include genetic factors, intrauterine exposures, environmental/lifestyle factors and obesity.^[6]

PCOS is characterised by hyperandrogenaemia and hyperinsulinaemia.^[7] The high levels of androgens lead to chronic anovulation, menstrual disturbances and hirsutism. These patients typically have insulin resistance (IR). The hyperandrogenism is closely tied with the IR, and the decline in insulin levels leads to decreased androgen production.^[8-10] The associated IR leads to increased risk for developing glucose intolerance, type 2 diabetes mellitus and gestational diabetes mellitus.^[11,12]

Clinical manifestations of PCOS symptoms are often preceded by a history of weight gain.^[13] Overweight and obese women have been reported to have a high prevalence of PCOS.^[14] Between 40% and 80% of women with this condition are reported to be overweight or obese.^[15] Nearly 40% of women with PCOS are expected to have impaired glucose tolerance or overt type 2 diabetes, a finding that is consistently seen across several geographic areas and ethnic groups.^[16] Moreover, women with PCOS are more likely to have IR,^[17] central adiposity, dyslipidaemia and hypertension.^[18] Other markers of cardiovascular disease such as C-reactive protein^[19] and homocysteine^[20,21] have also been found to be elevated in women with PCOS.

Homocysteine, a sulfhydryl-containing amino acid, is an intermediate product in the normal biosynthesis of the amino acids methionine and cysteine.^[22] Elevated levels of circulating homocysteine increase the risk for developing atherothrombotic coronary artery disease, peripheral vascular disease, myocardial infarction (MI) and stroke.^[23] Interestingly, obesity, hyperinsulinaemia and hyperhomocysteinaemia have been shown to be associated with an increased risk of cardiovascular disease. Moreover, studies have shown a significant association between obesity and IR,^[24-26] obesity and homocysteine levels^[27,28] and insulin and homocysteine levels.^[29,30] However, whether these three cardiovascular risk factors having a high prevalence in PCOS are also interrelated is not established fully. It is also of interest to study the relationship between insulin and homocysteine levels with respect to body mass index (BMI) status of the PCOS women. Hence, the present study was planned to evaluate the correlation of serum homocysteine levels and hyperinsulinaemia with BMI in PCOS patients visiting a facility in North India.

MATERIALS AND METHODS

It was a case-control study done in the Department of Gynaecology, from June 2019 to May 2020, approved by the Institutional Ethical Committee (RCCell EC/2019/112 dated 15 May 2019).

Inclusion criteria

Cases

The patients were included on the basis of Rotterdam diagnostic criteria of PCOS.

Two of the following three criteria are required:

- i. Oligo/anovulation,
- ii. hyperandrogenism-clinical (hirsutism or less commonly male pattern Alopecia) or biochemical (Raised testosterone)
- iii. Polycystic ovaries on Ultrasound i.e presence of at least 12 follicles of 2-9 mm diameter and/or increased ovarian volume 10ml.

Controls

Age-matched women without PCOS were included in the study.

Exclusion criteria

Patients with pregnancy, hyperprolactenaemia, thyroid dysfunction, hypertension, gastrectomy, on medications for treatment of cardiovascular and coronary heart disease, patients on folate antagonist (methotrexate), phenytoin, carbamazepine and those on anti-obesity 27 drugs, contraceptive pills, smokers and chronic 28 alcoholics were excluded from the study.

Sample size calculation

Sample size was calculated on the basis of variation in serum homocysteine, plasma insulin levels and BMI to be studied as described by Esmailzadeh *et al.*^[31] Thus, a total of 70 participants – 35 each in case and control groups, respectively – were enrolled in the study.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the Helsinki Declaration (2013).

Written informed consent was obtained from all individual participants included in the study. The cases and controls underwent thorough clinical and biochemical investigations necessary to ascertain their fulfilment of sampling criteria. Age of women was noted and their weight and height were measured. The body mass index was calculated using the following formula:

$$\text{BMI} = \text{weight in kg/height in m}^2$$

On the basis of body mass index, the women were categorised into the following categories using the

definitions proposed by the WHO for Asian population.^[32] Fasting glucose, insulin and homocysteine levels were measured by direct chemiluminescence immunoassay. IR was measured in terms of homeostatic assessment of insulin resistance (HOMA-IR), which was calculated using the following formula:

$$\text{HOMA-IR} = \text{fasting insulin (microU/L)} \times \text{fasting glucose (nmol/L)} / 22.5.$$

For homocysteine and fasting insulin, the normal range was taken as 4.44–13.56 $\mu\text{mol/L}$ and 2.60–24.90 $\mu\text{U/mL}$, respectively.^[33] Homocysteine value $<4.44 \mu\text{mol/L}$ was considered hypohomocysteinaemia, whereas a value $>13.56 \mu\text{mol/L}$ was considered hyperhomocysteinaemia. For fasting insulin, a value $<2.60 \mu\text{U/mL}$ was considered hypoinsulinaemia and a value $>13.56 \mu\text{U/mL}$ was considered hyperinsulinaemia. IR was considered at HOMA-IR value >2.5 .^[23]

Statistical analysis

The statistical analysis was done using SPSS (Statistical Package for the Social Sciences) version 21.0 Statistical Analysis Software. The values were represented in number (%) and mean \pm standard deviation. Student's *t*-test was used to test the significance of two means and to compare the scores of each of the measures and some of the parameter data between the groups. Analysis of variance test was used to compare the within-group and between-group variances amongst the study groups. The Pearson correlation coefficient was then used to estimate of the correlation between paired data sets and its value ranges from -1 to $+1$, with $+1$ indicating perfect positive correlation and -1 indicating perfect negative correlation. A *P* value of ≤ 0.05 was considered statistically significant.

RESULTS

Cases had significantly higher mean fasting glucose and insulin levels (94.06 mg/dl \pm 10.27 mg/dl and 23.35 $\mu\text{U/ml}$ \pm 33.35 $\mu\text{U/ml}$, respectively) as compared to that of controls (81.77 mg/dl \pm 8.82 mg/dl and 11.09 $\mu\text{U/ml}$ \pm 12.05 $\mu\text{U/ml}$, respectively) ($P < 0.05$). Mean HOMA-IR and homocysteine levels were 5.61 ± 8.56 and $17.93 \mu\text{mol/L} \pm 9.86 \mu\text{mol/L}$, respectively, in cases and 2.29 ± 2.63 and $10.32 \mu\text{mol/L} \pm 5.95 \mu\text{mol/L}$, respectively, in controls; both the values were significantly higher in cases as compared to that in controls. The prevalence of hyperinsulinaemia, IR and hyperhomocysteinaemia was 11.4%, 65.7% and 62.9%, respectively, in cases as compared to 5.7%, 28.6% and 20%, respectively, in controls. A statistically significant difference between the two groups was observed for IR and hyperhomocysteinaemia, respectively ($P < 0.05$) [Table 1].

On overall evaluation, there was a significant incremental trend of IR with increasing body mass index ($P < 0.001$). On comparing the cases and controls for prevalence of IR amongst different BMI categories, although the prevalence of IR was found to be higher in cases as compared to controls in all the BMI categories, this difference was significant statistically for overweight and obese categories ($P < 0.05$) but not for normal weight category ($P = 0.115$). The prevalence of hyperinsulinaemia showed a significant difference amongst different BMI categories ($P = 0.010$). Hyperhomocysteinaemia was found to be higher in cases as compared to that in controls in all the BMI categories, however, the difference was significant statistically only for overweight and obese categories ($P < 0.05$) [Table 2]. On evaluating the correlation of BMI with different markers, on overall evaluation, a significant positive correlation of all the four markers (fasting glucose,

Table 1: Comparison of characteristics of cases and controls

Characteristic	Cases (n=35)	Controls (n=35)	Significance of difference
Mean age \pm SD (years)	23.94 \pm 4.45	23.83 \pm 4.64	$t=0.105$; $P=0.917$
Mean BMI \pm SD (kg/m ²)	27.61 \pm 5.74	25.37 \pm 4.35	$t=1.842$; $P=0.070$
BMI category (kg/m ²), n (%)			
Normal weight (18.5-22.9)	9 (25.7)	10 (28.6)	$\chi^2=0.545$; $P=0.762$
Overweight (23-24.9)	10 (28.6)	12 (34.3)	
Obese (>25.0)	16 (45.7)	13 (37.1)	
Mean fasting glucose \pm SD (mg/dl)	94.06 \pm 10.27	81.77 \pm 8.82	$t=5.369$; $P<0.001$
Mean fasting insulin \pm SD ($\mu\text{mol/L}$)	23.35 \pm 33.35	11.09 \pm 12.05	$t=2.034$; $P=0.046$
Hyperinsulinaemia, n (%)	4 (11.4)	2 (5.7)	$\chi^2=0.729$; $P=0.393$
Mean HOMA-IR \pm SD	5.61 \pm 8.56	2.29 \pm 2.63	$t=2.191$; $P=0.032$
Insulin resistance, n (%)	23 (65.7)	10 (28.6)	$\chi^2=9.689$; $P=0.002$
Mean Hcy \pm SD ($\mu\text{mol/L}$)	17.93 \pm 9.86	10.32 \pm 5.95	$t=3.911$; $P<0.001$
Hyperhomocysteinaemia, n (%)	22 (62.9)	7 (20.0)	$\chi^2=13.25$; $P<0.001$

SD=Standard deviation, BMI=Body mass index, HOMA-IR=Homeostatic assessment of insulin resistance

fasting insulin, HOMA-IR and serum homocysteine) was observed ($P < 0.05$), however, on evaluating the correlation of these markers independently in cases and controls, the only fasting insulin and HOMA-IR showed a significant correlation [Table 3]. In a multivariate model where PCOS was considered a dependent variable with age, fasting glucose, HOMA-IR, serum homocysteine and body mass index as the independent variables, only serum homocysteine levels were found to be significantly associated with the dependent variable (odds ratio = 1.172; 95% confidence interval = 1.032–1.330). The predicted model had a high classifying ability with sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 82.9%, 80%, 80.6%, 77.8% and 81.4%, respectively [Table 4].

DISCUSSION

In the present study, the purpose was to study the relationship of serum homocysteine, IR and serum homocysteine levels in PCOS patients. Three major considerations were kept in mind while planning the study – (i) whether insulin and homocysteine levels in PCOS women are different from age- and BMI-matched non-PCOS women, (ii) whether insulin and homocysteine levels show a relationship with BMI and (iii) how does presence of PCOS affect the relationship of BMI, homocysteine and IR. For these considerations, a stratified sampling design with adequate representation of PCOS women in different body mass index categories was the best choice,^[34,35] however, owing to practical difficulties, such a design

Table 2: Comparison of insulin resistance, hyperinsulinaemia and hyperhomocysteinaemia in relation to different body mass index categories

Weight category	Insulin resistance (HOMA-IR >2.5)						Statistical significance χ^2 -test (cases vs. controls)
	Overall		Cases		Controls		
	Total	IR (%)	Total	IR (%)	Total	IR (%)	
Normal	19	2 (10.5)	9	2 (22.2)	10	0	$\chi^2=2.484$; $P=0.115$
Overweight	22	6 (27.3)	10	5 (50.0)	12	1 (8.3)	$\chi^2=4.774$; $P=0.029$
Obese	29	25 (86.2)	16	16 (100)	13	9 (69.2)	$\chi^2=5.711$; $P=0.017$
Inter-BMI category statistical significance	$\chi^2=31.47$; $P<0.001$		$\chi^2=17.0$; $P<0.001$		$\chi^2=16.939$; $P<0.001$		

Weight category	Hyperinsulinaemia						Statistical significance Cases versus controls (Student's <i>t</i> -test)
	Overall		Cases		Controls		
	Total	Hyper insulin	Total	Hyper insulin	Total	Hyper insulin	
Normal	19	0	9	0	10	0	-
Overweight	22	0	10	0	12	0	-
Obese	29	6 (20.7%)	16	4 (25.0%)	13	2 (15.4%)	$\chi^2=0.404$; $P=0.525$
Inter-BMI category statistical significance	$\chi^2=9.278$; $P=0.010$		$\chi^2=5.363$; $P=0.068$		$\chi^2=3.590$; $P=0.166$		

Weight category	Hyperhomocysteinaemia						Cases versus controls
	Overall		Cases		Controls		
	Total	Hyper HCy (%)	Total	Hyper HCy (%)	Total	Hyper HCy (%)	
Normal	19	2 (10.5)	9	1 (11.1)	10	1 (10.0)	$\chi^2=0.006$; $P=0.937$
Overweight	22	10 (45.5)	10	7 (70.0)	12	3 (25.0)	$\chi^2=4.455$; $P=0.035$
Obese	29	17 (58.6)	16	14 (87.5)	13	3 (23.1)	$\chi^2=12.272$; $P<0.001$
Inter-BMI category statistical significance	$\chi^2=11.157$; $P=0.004$		$\chi^2=14.702$; $P=0.001$		$\chi^2=0.889$; $P=0.641$		

BMI=Body mass index, HOMA-IR=Homoeostatic assessment of insulin resistance, IR=Insulin resistance

Table 3: Correlation of body mass index with fasting glucose, fasting insulin, homoeostatic assessment of insulin resistance and serum homocysteine levels

Parameter	Overall (n=70)		Cases (n=35)		Controls (n=35)	
	r	P	r	P	r	P
Fasting glucose	0.283	0.018	0.190	0.274	0.192	0.268
Fasting insulin	0.381	0.001	0.353	0.038	0.372	0.028
HOMA-IR	0.373	0.001	0.348	0.040	0.360	0.034
Serum Homocysteine	0.356	0.002	0.296	0.084	0.281	0.102

HOMA-IR=Homoeostatic assessment of insulin resistance

Table 4: Multivariate binary logistic regression analysis showing polycystic ovary syndrome as a dependent variable on independent variables age, body mass index, serum fasting glucose, serum fasting insulin and serum homocysteine levels

Variables	B	SE	Wald statistic	P	OR	95.0% CI for OR	
						Lower	Upper
Age	0.044	0.068	0.407	0.524	1.045	0.914	1.194
Fasting glucose	0.093	0.060	2.411	0.120	1.098	0.976	1.234
Fasting insulin	-0.107	0.353	0.091	0.763	0.899	0.450	1.796
HOMA-IR	0.522	1.594	0.107	0.743	1.685	0.074	38.340
Serum homocysteine	0.158	0.065	5.977	0.014	1.172	1.032	1.330
BMI	-0.032	0.079	0.159	0.690	0.969	0.829	1.132
Constant	-10.626	5.612	3.585	0.058	<0.001		

Classification table based on binary logistic regression

Projected group	Group		Total
	PCOS	Controls	
PCOS	29	7	36
Controls	6	28	34

Classifying efficacy of predictive model

Sensitivity	Specificity	PPV	NPV	Accuracy
82.9	80.0	80.6	77.8	81.4

BMI=Body mass index, SE=Standard error, OR=Odds ratio, CI=Confidence interval, HOMA-IR=Homoeostatic assessment of insulin resistance, PCOS=Polycystic ovary syndrome, PPV=Positive predictive value, NPV=Negative predictive value

could not be adopted, and within PCOS women, the representation of different body mass index categories was governed randomly. A study of body mass index, IR and homocysteine levels amongst PCOS women has been done amongst a diverse profile of patients in different studies. Table 5 highlights the findings of some of the contemporary studies and compares them with the present study. An overview of Table 5 shows that the age of cases ranges from as low as 23.13 ± 4.28 years to as high as 31.09 ± 8.9 years^[36] while the mean BMI of cases ranged from $22.31 \text{ kg/m}^2 \pm 5.04 \text{ kg/m}^2$ to $29.95 \text{ kg/m}^2 \pm 4.91 \text{ kg/m}^2$ (Esmailzadeh *et al.*^[31]). In studies having matched age and BMI as well as in studies having matched age but higher BMI of PCOS women, the serum homocysteine levels were found to be significantly higher in PCOS women as compared to controls, thus indicating that presence of PCOS itself was a strong factor associated with increased homocysteine levels and thus increased homocysteine levels in PCOS women cannot be attributed just to the increased BMI. Only one study, Bagheri *et al.*^[35] despite having cases with significantly higher BMI as compared to controls, did not find a significant difference in mean homocysteine levels. Most of the studies reported above have also evaluated fasting insulin and HOMA-IR between two groups and have reported these values to be significantly higher in the case group as compared to controls as observed in the present study,^[31,37,39] thus implying that irrespective of the BMI status, it is primarily the PCOS status that affects the homocysteine levels in PCOS. Esmailzadeh

et al.^[31] also showed that there was a tendency towards hyperhomocysteinaemia and hyperinsulinaemia in PCOS patients, with as high as 76.7% of cases being insulin resistant, thus indicating a relationship between hyperhomocysteinaemia and IR. All these findings indicate that the trends of IR and homocysteinaemia are affected by PCOS presence. We have found that mean HOMA-IR, homocysteine and fasting insulin levels showed a significant incremental trend with increasing BMI category in overall evaluation as well as in cases and controls, underlining the two facts – first, presence of PCOS itself was a strong factor affecting IR and homocysteine levels, and second, BMI does have some relationship with IR and homocysteine levels. Moreover, an existence of relationship between BMI, IR and homocysteine independently in cases as well as controls showed that this relationship is universal irrespective of the PCOS status. This implies that obese patients with PCOS are at a multiplied risk of developing hyperhomocysteinaemia and IR and thus in turn cardiovascular disease. The relationship of obesity with IR and homocysteine levels extends beyond PCOS, as have also been shown by previous studies.^[34,35] The findings of the present study replicate these previous studies with respect to their relationship with homocysteine levels between cases and controls in different BMI categories.

Some of the previous studies have also evaluated relationship of BMI with these parameters in linear terms. Guzelmeric *et al.*^[40] in their study also found a

Table 5: Body mass index, insulin resistance and homocysteine in polycystic ovary syndrome as observed in different contemporary studies compared to the present study

Author (year), location	Sample size and study design	Characteristic	Cases	Controls
Bagheri <i>et al.</i> (2015), Iran ^[35]	Case-control (52 cases, 104 controls)	Age (years)	24.27±3.75	25.62±4.32
		BMI (kg/m ²)	25.80±6.67*	22.60±2.87
		Insulin (µIU/ml)	16.62±7.45*	12.04±4.24
		HOMA	33.72±14.74*	44.56±16.94
		Homocysteine (µmol/l)	12.21±4.55	13.68±4.31
Al-Gareeb <i>et al.</i> (2016), Iraq ^[36]	Case-control (101 cases, 106 controls)	Age (years)	24.86	25.41
		BMI (kg/m ²)	60% >25*	22.6% >25
		Homocysteine (µmol/l)	11.5±5.41*	8.10±1.89
Esmailzadeh <i>et al.</i> (2017), Iraq ^[31]	Case-control (60 cases, 20 controls)	Age (years)	23.65±5.08	23.73±3.85
		BMI (kg/m ²)	29.95±4.91*	26.09±4.80
		Insulin (µU/dl)	17.80±8.02*	11.55±6.81
		HOMA-IR	3.91±1.86*	2.49±1.63
		Homocysteine (µmol/l)	11.68±2.92*	9.31±2.92
Saadeh <i>et al.</i> (2018), Iraq ^[37]	Case-control (154 cases, 151 controls)	Age (years)	23.85±5.12	24.35±5.10
		BMI (kg/m ²)	26.57±5.98	26.23±5.82
		Homocysteine (µmol/l)	29.03±11.80*	14.23±5.53
Suleiman and Sulaiman (2018), Jordan ^[38]	Case-control (50 cases, 40 controls)	Age (years)	26.88±6.76	27.17±5.24
		BMI (kg/m ²)	27.17±5.24*	24.24±3.39
		Homocysteine (µmol/l)	17.00±4.00*	9.00±2.15
Present study (2020), Lucknow, India	Case-control (35 cases, 35 controls)	Age (years)	23.94±4.45	23.83±4.64
		BMI (kg/m ²)	27.61±5.74	25.37±4.35
		Insulin (µU/dl)	23.35±33.35*	11.09±12.05
		HOMA-IR	5.61±8.56*	2.29±2.63
		Homocysteine (µmol/l)	17.93±9.86*	10.32±5.95

*A significant difference between cases and controls, BMI=Body mass index, HOMA-IR=Homoeostatic assessment of insulin resistance

significant mild positive correlation of homocysteine with BMI ($r = 0.349$) which is close to the value obtained in the present study ($r = 0.356$, overall, $r = 0.296$ PCOS group). In another study, Esmailzadeh *et al.*^[31] also observed a near-moderate ($r = 0.46$) correlation of BMI with HOMA-IR. In the present study, we found this correlation to be 0.373 in overall and 0.348 in PCOS women. In the present study, we also found a significant correlation of BMI with fasting insulin ($r = 0.381$ – overall, $r = 0.353$ – PCOS).

The present study had certain limitations; owing to limitation of sample size, the stratification of different BMI categories could not be done at a level at which the differences based on BMI could be elaborated statistically in a more convincing manner. Moreover, the analytical case-control nature of the study was a barrier in exploring the multifactorial relationship of PCOS, BMI, IR and hyperhomocysteinaemia. Consecutively, dietary factors and nutritional deficiencies also have a role in determination of PCOS and Vitamin B12 levels. Inclusion of such parameters could have helped in understanding the relationship of PCOS, BMI, IR and hyperhomocysteinaemia in a better way. Nevertheless, within these limitations, the findings of the present study showed that both BMI

and presence of PCOS were linked with IR as well as hyperhomocysteinaemia.

CONCLUSION

PCOS women had significantly higher mean fasting glucose, fasting insulin, HOMA-IR and homocysteine levels as compared to non-PCOS controls. The prevalence of IR and hyperhomocysteinaemia was significantly higher in PCOS women as compared to non-PCOS controls. Mean HOMA-IR, homocysteine and fasting insulin levels showed a significant incremental trend with increasing BMI category in overall evaluation as well as in cases and controls independently. Fasting insulin and HOMA-IR also showed a significantly mild positive correlation with BMI in cases and controls when evaluated individually.

Data availability statement

All the data are available with the corresponding author and will be willingly shared on reasonable requests.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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