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Correlation between elevated homocysteine levels and insulin resistance in infertile women with or without polycystic ovary syndrome in North Indian population

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting about 5 to 10% women of reproductive age group worldwide. This study was designed to examine the relationship between elevated homocysteine levels and insulin resistance (IR) in infertile women with or without PCOS. This cross sectional case control study was conducted in Department of Obstetrics and Gynaecology, Pathology and Medicine, CSM Medical University (Erstwhile KGMU), Lucknow, UP India. After informed consent, a total 90 infertile women were enrolled which included 50 diagnosed cases of PCOS according to Rotterdam consensus meeting 2003 and 40 healthy non PCOS as controls. Mean plasma homocysteine levels were significantly higher in PCOS women (11.8796±5.5) as compared to non PCOS women (7.8095±2.2). Obesity was found in 64% PCOS women and 37.5% of non PCOS women which was significant. Serum testosterone levels were elevated in 42% of PCOS women, but none of the women of non PCOS group had elevated testosterone levels. Amongst the PCOS patients (32/50), 64% were IR and (18/50) 36% were non insulin resistance (NIR) PCOS group which was stratified by HOMA-IR. Thirty-two women had mean HOMA-IR (5.95±1.27) designated PCOS IR and 18 had mean HOMA-IR (1.86±0.028) designated PCOS NIR. Elevated body mass index (BMI) was not significantly associated with IR in PCOS patients. BMI in PCOS IR was 27.43±3.096 and BMI in PCOS NIR was 25.728±2.609 (P<0.07). Homocysteine levels were significantly elevated in PCOS patients (mean 11.87±5.5) (All PCOS), IR PCOS (13.82±5.69 pmol/q) versus controls (7.80±2.29 pmol/L) (P<0.001). In conclusion, obesity is not an independent risk factor to increase plasma homocysteine levels in PCOS women.

Key words: Homocysteine, polycystic ovary syndrome, insulin resistance, infertility.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting about 5 to 10% women of reproductive age group worldwide. It is also estimated to be the major cause of anovulatory infertility accounting for about 73% of cases. Variance in prevalence among population is thought to be dependent on ethnic origin, race and other environmental factors on the phenotype Ehrmann (2005). The exact aetiology of PCOS remains unknown, but hyperandrogenism was thought to be a main underlying factor. Now, the syndrome is thought to have wider

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metabolic and cardiovascular implications. Plienotypic manifestations of the syndrome vary from patient to patient and a Rotterdam diagnostic criteria for PCOS is based on the clinical identification of at least two of the three defined criteria which include: (1) oligo/anovulation, (2) chemical and/or biochemical evidence of hyper androgenemia and (3) ultrasonographic findings of polycystic ovaries (Pehlivanov and Orbetzova, 2007; The Rotterdam ESHRE/ASRIVI sponsored PCOS consensus workshop group revised, 2003).

Elevated levels of plasma homocysteine have been implicated as a significant risk factor for cardiovascular disease, preeclampsia and recurrent pregnancy loss (Del Bianco et al. 2004).

Homocysteine is an intermediate substance formed during the breakdown of the amino acid methionine and may undergo remethylation to methionine or trans-sulfuration to cystathione and cysteine. Recent research has pointed to many non-enzymatic factors which may influence homocysteine levels including age, gender, or sex-steroid environment (IVIcCarty 2000a).

Insulin levels have also been implicated as a modulating factor of homocysteine in which insulin inhibits hepatic cystathionine P-synthase activity (Schneede et al. 2000). Hence, elevated levels of liomocysteine have been positively associated with insulin levels in a number of clinical situations. PCOS a common endocrinopathy in women of reproductive age group is a multifaceted metabolic disease (IVIcCarty 2000a; Schneede et al. 2000). Plasma levels of insulin seem to influence homocysteine metabolism, possibly through effects on glomerular filtration or by influencing the activity of key enzymes in homocysteine metabolism (Giltay et al. 1998; GallistI et al. 2000). Thus, it seems logical to hypothesize that elevated homocysteine levels could be another feature of PCOS both being associated with IR and reproductive failure (Craig et al. 2002). Insulin resistance (IR) has been found in up to 70% of women with PCOS and is a risk factor for development of type II diabetes mellitus in these women (Laivuoriet al.1999). Several studies have investigated the association of homocysteine levels in PCOS patients. Because of complex limitations of these studies, such as lack of uniformity in the definition of PCOS and information on levels of other cofactors, the results vary. Thus, this study was designed to examine the relationship between elevated homocysteine levels and IR in infertile women with or without PCOS.

MATERIALS AND METHODS

This cross sectional case control study was conducted in Department of Obstetrics and Gynaecology, in collaboration with Department of Pathology and Medicine, CSM Medical University, Lucknow, UP, India. After informed consent, a total of 90 infertile women were enrolled which included 50 diagnosed cases of PCOS according to Rotterdam European Society of Human Reproduction and Embryology Consensus Meeting 2003 guideline and 40 healthy non PCOS infertile women were taken as controls. Ethical clearance clearance was obtained from Institutional Ethics Committee.

Exclusion criteria for all subjects including current or previous use of oral contraceptive pills (within 6 months), drugs like metformin, phenytoin, folic acid, vitamins, antiandrogens, antidiabetics, statin, glucocorticoids, cigarette smoking, chronic alcohol consumption, coffee consumption more than 2 cups/day known case of hypertension, diabetes mellitus and cardiovascular disease. All subjects were asked to keep their normal diet and not to perform any sport like activity; same exclusion criteria as case group were used for control group. The entire women were subjected to thorough physical examination and laboratory tests.

All blood samples were obtained in the morning on the 2nd day of menstruation after an overnight fasting. During the same visit, all subjects underwent anthropometric measurement. The serum concentration of follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, prolactin and thyroid-stimulating hormone (TSH) were measured by Chemiluminescent enzyme immunoassay (Immulite 2000 diagnostic product corporation LA, CA). Serum glucose was measured using glucokinase technique. Plasma insulin levels were measured by Chemiluminescent enzyme immunoassay (Immulite 1000 analyzer with inter-assay and intra- assay coefficient of variation did not exceed 6.4%). Blood samples for homocysteine measurement were collected, and were immediately placed on ice and were centrifuged at 4°C. Plasma was separated within 30 min and was stored at -70°C. Plasma homocysteine concentration was measured by fluorescence polarization immunoassay by using ABBOTT diagnostic kit (USA). Normal reference range of our laboratory were 5 to 11 pmol/L. Hyperhomocysteinemia was defined as plasma homocysteine level >11 pmol/L. IR was determined by a number of different methods including, fasting insulin, fasting glucose to insulin ratio and HOMA- IR. HOMA-IR >2.5 was considered as IR. The estimation of IR by HOMA score was calculated with the formula, fasting serum insulin (pU/ml X fasting plasma glucose (mmol/L)/ 22.5). BMI was calculated as the weight in kilograms divided by the square of the height in metres (kg/m).

The data were subjected to statistical analysis by Statistical Package for Social Sciences (SPSS-16) version. The difference between two groups was assessed by independent 't' test and probability was calculated on the basis of associated degree of freedom. 95% confidence level has been chosen and P value <0.05 was considered as significant. Pearson's correlation coefficients were used to calculate correlation between paired data sets. Significance of correlation and the relative contribution of each variable were calculated.

RESULTS

All the subjects included in this study were matched for age, religion, dietary habits and socioeconomic status. Hirsutism is one of the common clinical features of PCOS. In our study 56% of PCOS women had hirsutism as compared to 12.5% controls had hirsutism (P<0.001). Mean plasma homocysteine levels were significantly higher in PCOS women (11.88±5.5) as compared to non PCOS women (7.81 ±2.2) (P<0.001). Obesity was found in 64% PCOS women as compared to 37.5% of non PCOS women which was significant (P<0.001). Serum testosterone levels were elevated in 42% of PCOS women, but none of the women in the control group had elevated testosterone levels (P<0.001) Table 1.

IR definitions

IR was defined as an abnormal result in fasting insulin,

Table 1. Clinico-demographic profile of the subjects.

Profile	Case (%)	Control (%)	P value
Normal	50	40	-
Mean age (years)	26.10±4.08	27.01±4.28	0.299
Infertility Primary	84.4	77.5	0.08
Secondary	15.6	22.5	
Religion wise Hindu	74	77.5	
Muslim	26	22.5	0.7
Dietary habits vegetarian	66	60	
Non vegetarian	34	40	0.557
Socio-economic status wise distribution	80	77.5	0.773
Middle and higher lower	20	22.5	
Distribution of subjects according to menstrual abnormality			
Oligomenorrhea	38	-	
Prolong	42	-	-
Normal	20	100	
Distribution of subjects according to hirsutism			
Present	56	12.5	0.001
Absent	44	87.5	
Occupation			
Housewife	82.2	70.0	-
Working	17.8	30.0	
Mean plasma homocysteine level	11.88±5.55	7.80±2.29	<0.001
BMI			
<25	36	62.5	<0.001
≥25	64	37.5	
S.LH/FSH ratio			
<2.5	48	97.5	<0.001
≥2.5	52	2.5	
S. Testosterone (ngm/dL)			
<80	58	100	<0.001

glucose: insulin ratio or HOMA-IR value, determined by calculating threshold values >95th percentile of the normal control group. These were fasting insulin (>20mIU/L), glucose insulin ratio (GI<4.5) and HOMA-IR value (>2.5). Thus, IR was found in 56% of PCOS women by fasting insulin and in 60% of PCOS patients by glucose insulin ratio and in 64% of PCOS patients by HOMA-IR all statistically significant as compared to normal controls (P<0.001).

Thus, HOMA-IR is one of the most sensitive indicators to determine IR. Amongst the PCOS patients (32/50), 64% were insulin resistant and (18/50) 36% were non insulin resistant (NIR) PCOS group which was stratified by HOMA-IR. 32 women had mean HOMA-IR (5.95±1.27)

Table 2. Clinical and biochemical data of all patient, PCOS stratified by insulin resistance.

Parameter	No.	Age	BMI	LH/FSH	Insulin	G/I ratio	HOMA	Plasma Hcy
Reference range	-	-	≤25	<2.5	<20 mIU/L	>4.5	<2.5	5-11<11 µmol/L
Case (all PCOS)	50	26.10±4.08	26.82±3.665	2.294±0.963	21.07±9.69	5.34±3.02	4.48±2.23	11.87±5.55
PCOS, NIR	18	26.56±4.48	25.7289±2.60906	1.67±0.65	9.25±1.35	9.09±1.59	1.86±.28	8.24±.77
PCOS, IR	32	25.84±4.39	27.438±3.996	2.64±0.89	27.62±4.71	3.23±.57	5.95±1.27	13.82±5.69
P value IR								
PCOS versus NIR PCOS	-	NS	0.07^{NS}	0.000	0.000	0.000	0.000	<0.001
Control	40	27.02±4.28	24.65±2.62	0.98±.60	7.53±3.55	11.68±3.02	1.83±2.25	7.80±2.29
P value PCOS IR versus control	-	NS	<0.001	<0.001	<.0.001	<0.001	<0.001	<0.001
P value PCOS NIR versus control		NS	0.237^{NS}	<0.002	0.110^{NS}	<0.001	0.947^{NS}	0.700^{NS}

designated PCOS IR and 18 had mean HOMA-IR (1.86±0.028) designated PCOS NIR (Table 2).

After statistical analysis, it was found out that there was no association of IR with age and BMI in PCOS women. However, elevated HOMA index was found to be significantly associated with higher LH/FSH ratio, insulin levels, glucose:insulin ratio and elevated plasma homocysteine (Table 2). In other words, IR correlated positively with homocysteine in PCOS women.Cystathionine-β-synthase, the key enzyme of the transsulfuration pathway in homocysteine metabolism, is down regulated in an insulin resistant state.

Body weight and other variables

PCOS patients were found to be more obese than controls. When patients were stratified by BMI, 64% (32/50) PCOS patients had a BMI ≥25 kg/m^2, whereas only 37.5% (16/40) of controls group had a BMI ≥25 kg/m2. Elevated BMI was not significantly associated with IR in PCOS patients. BMI in PCOS IR was 27.43±3.096 and BMI in PCOS NIR was 25.728±2.609 (P<0.07) (Table 2). Elevated LH/FSH ratio was significantly associated with PCOS state whether obese or non obese, IR or NIR (Tables 2 and 3). Homocysteine as related to other variables Homocysteine levels were significantly elevated in all PCOS patients (mean 11.87±5.5 µmol/L), in IR PCOS (13.82 ± 5.69 µmol/L) versus controls (7.80±2.29 µmol/L), (P<0.001) (Table 2). Elevated homocysteine was noted in both non obese and obese PCOS as opposed to non obese and obese controls (9.4±3.10; 13.2±6.17 versus 7.5±1.53; 8.29±3.1; P<0.001) (Table 3). The 95th percentile for homocysteine in our control group was 11.0 µmol/L, when a level of 11 µmol/L was used as a threshold, 36% of PCOS patient had homocysteine value more than normal cutoff value, (P<0.001) (Table 3). Out of 18 NIR PCOS patients, only 5 (22.7%) had elevated homocysteine level (>11 µmol/L), whereas 32(40.6%) IR PCOS had an elevated homocysteine levels demonstrating the differential effect of IR on homocysteine (Table 4). When we had compared non obese control with non obese PCOS patients, these two groups were found to have insignificant different BMI, but significant differences in IR and homocysteine levels. Non obese PCOS patients had higher homocysteine levels than non obese controls (9.4±3.10; 7.50±1.53) (Table 3). Thus, body weight was not found to be predictor of homocysteine, rather IR regardless of body weight correlated with homocysteine levels.

Multiple comparison analysis was done among plasma homocysteine, IR (PCOS), NIR (PCOS) and controls. Comparison analysis strongly suggests that IR have strong correlation for high plasma homocysteine in patients of PCOS (Table 5). Correlation of different clinical and laboratory parameters was examined. Clinical and biochemical criteria were examined. A strong positive correlation was found between HOMA IR and insulin levels (r~0.987) and moderate positive correlation was observed between HOMA IR and BMI, homocysteine levels and serum LH and FSH ratio. Positive correlation was also observed with glucose levels and serum testosterone levels (Table 6). No association was found between age and PCOS, age and IR or age and homocysteine

Table 3. Comparison of clinical and biochemical properties of infertile women as stratified as body mass index (BMI).

Parameter [no.]	Reference range						
	Mean age ± SD	BMI < 24.9	LH/FSH < 2.5	Insulin < 20 (mIU/L)	G/I > 4.5	HOMA < 2.5	HCY ≤ 11
PCOS (Non-obese) [18]	26.0±4.07	23.0±1.58	2.2±0.94	17.8±8.1	5.8±2.69	3.94±1.81	9.4±3.10
PCOS (Obese) [32]	26.2±4.15	38.9±2.56	2.3±0.99	22.6±10.3	5.2±3.19	4.69±2.43	13.2±6.17
Control (Non-obese) [24]	27.1±4.88	23.0±1.14	0.95±0.56	6.8±1.34	12.3±2.42	1.34±0.28	7.50±1.53
Control (Obese) [16]	26.9±3.3	27.2±2.07	1.03±0.67	8.7±5.27	10.8±3.64	1.95±1.36	8.27±3.11
Statistical Significance "p"	0.773	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PCOS obese versus PCOS non-obese	0.898	<0.001	0.696	0.097	0.494	0.260	0.018
PCOS obese versus control obese	0.500	0.028	<0.001	<0.001	<0.001	<0.001	0.004
PCOS obese versus control non-obese	0.427	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PCOS non-obese versus control non-obese	0.433	0.987	<0.001	<0.001	<0.001	<0.001	0.011

Table 4. Clinical and Biochemical Data for all patients using normal homocysteine as illustrated values are Mean±SD.

Group	No. (%)	BMI	LH/FSH	Insulin (mIU/L)	G/I	HOMA	HCy
HCy<11 (Control)	36 (90)	24.17± 2.06	0.98±0.63	6.79±1.29	12.04±2.50	1.43±0.65	7.23±1.52
HCy<11 (PCOS)	32 (64)	25.52±3.40	1.93±0.91	18.56±8.64	6.09±3.04	3.75±1.84	8.29±1.71
HCy≥11 (Control)	4 (10)	29.53±2.20	0.97±0.12	14.29±8.80	8.42±5.48	2.97±1.81	13.03±1.01
HCy≥11 (PCOS)	18 (36)	29.09±2.88	2.94±0.69	24.87±10.56	4.14±2.59	5.62±2.43	18.26±4.01
"P"	–	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Clinical and biochemical data for patients with different homocysteine levels in different groups revealed a statistically significant intergroup difference for all the parameters being studied (P<0.001).

Table 5. Multiple comparison analysis: Plasma homocysteine comparison among IR (PCOS), NIR (PCOS) and control **1 (NIR, PCOS), 2 (IR, PCOS), 3 (Control).

Dependent variable	Homagr	Homagr	Mean difference (I-J)	Standard error	Sig.	95% Confidence interval	
						Lower bound	Upper bound
NIR versus IR	1	2	-5.68601*	1.15737	0.000	-7.986	-3.3856
		3	0.43106	1.11492	0.700	-1.785	2.6471
IR versus Control	2	1	5.68601*	1.15737	0.000	3.3856	7.9864
		3	6.11706*	0.93166	0.000	4.2653	7.9688
NIR versus control	3	1	-0.43106	1.11492	0.700	-2.6471	1.7850
		2	-6.11706*	0.93166	0.000	-7.9688	-4.2653

The statistics value shown in the table strongly suggest insulin resistance have strong correlation for high plasma homocysteine in patient of PCOS.

Table 6. Correlation of different clinical and laboratory parameters with HOMA index.

Parameter	Value
Insulin	r~0.987
BMI	r~0.50
Homocysteine	r~0.51
S.FSH/LH ratio	r~0.57

level.

DISCUSSION

PCOS associated infertility has been attributed to various factors including oligo-anovulation, dysfunctional gonadotropin secretion, hyperandrogenemia and dysfunction of any or several ovarian growth factors and their binding proteins. The clinic-demographic profile of both PCOS and non PCOS patients were similar except that the prevalence of obesity was more amongst PCOS patients (62.5%) as compared to controls (37.5%).

Recent research has focused on systemic and local effect of IR and homocysteine and its secondary effects on reproductive system. Recently in literature, it has been reported that PCOS is not only the most common reproductive disorder, but also a pleurimetabolic syndrome (Scarpitta and Sinagra 2000). Previous studies have found an association between IR and elevated homocysteine in specific patients groups in women of reproductive age. It is of interest to note that in our study, elevated homocysteine was best correlated to HOMA index out of three indices used for IR. Other authors have examined the relationship between plasma homocysteine levels and IR in patients with PCOS.

Elevated homocysteine was related to IR in women with preeclampsia, but not in normal controls (Laivuori et al. 1999). In this study, IR were higher in PCOS women as compared to non PCOS, but no significant difference was found in IR between obese and non obese PCOS women, this might be due to small sample size. While others reported that mean fasting insulin level was significantly higher in women with PCOS than controls. IR indices were significantly different between PCOS and controls, as well as obese PCOS patients as opposed to non obese PCOS, although both obese and non obese PCOS patients were more IR than normal healthy control (Ilhan et al. 2005).

Few studies reported a positive correlation between BMI and IR in premenopausal women; however, in this study IR was not related with BMI in PCOS women and it was independently associated with PCOS (Tanrikulu-Kilic et al.2006). In our study, IR indices were not significantly different in obese PCOS as compared to non obese PCOS, but there were more insulin resistant as compared to healthy controls. This means IR in patients with PCOS is associated with elevated plasma homocysteine regardless of body weight.

In this study, the mean serum fasting insulin, HOMA IR and homocysteine were significantly higher in PCOS group and results were highly similar to study done by other author (Mesut et al. 2009).

Moderate hyperhomocysteinemia has been found to be a risk factor for recurrent early pregnancy loss. Despite several pathophysiological hypotheses including impaired cell proliferation, increased oxidative stress, apoptosis, reduced extra-embryonic vascular development and hypomethylation, it is not clear whether hyperhomocysteinemia is causally related to recurrent early pregnancy loss or whether it is only a marker of increase risk of recurrent early pregnancy loss (Latacha and Rosenquist 2005). Elevated homocysteine may impair implantation by interfering with endometrial blood flow, vascular integrity and has been documented to increase the probability of early pregnancy loss (Del Bianco et al. 2004).

Both impaired implantation and increased rates of miscarriage are more frequent in PCOS women even after controlling ovulatory abnormalities, increased LH, and hyperandrogenism, which might be due in part to elevated homocysteine in these patients. Various studies have examined the association between plasma homocysteine levels and IR in his specific population of patients with PCOS. They reported that mean serum homocysteine concentrations are increased in women with PCOS as compared to controls (Ilhan et al. 2005).

Similarly, mean homocysteine levels were higher in PCOS women as compared to non PCOS here. When patients were stratified by body mass index, the homocysteine levels were significantly higher in obese and non obese PCOS as compared to controls (PCOS obese=13.2±6.17, PCOS non obese=9.4±3.10, obese controls=8.27±3.11, non obese controls=7.50±1.53) and similar conclusion were drawn by other study (Ilhan et al. 2005). Another study reported elevated homocysteine levels in PCOS patients and no significant difference was found regarding IR in obese and non obese PCOS. However, in PCOS women serum insulin levels and HOMA IR valuesm are significantly higher as compared to controls, similar to those in this study (Ahmed et al. 2007). Yarali et al. (2001) examined the cardiac diastolic dysfunction of PCOS patients as detected by echocardiography and have shown significantly higher plasma homocysteine concentration in both lean and obese PCOS patients than control group and this was related to IR (Yaraliet al. 2001). Schachter et al. (2003) also reported that IR and hyperinsulinemia in patients with PCOS was associated with elevated plasma homocysteine levels regardless of body weight (Schachter et al. 2003). Another study has shown that PCOS patients had elevated plasma homocysteine levels independent from their BMI (Loverro et al. 2002). In this study, significant association between plasma homocysteine levels and HOMA index was present; however, this is not in accordance with the findings of studies performed on large

healthy population Abbasi et al. 1999; Godsland et al.2001; Rosolova et al. 2002). The results of this study are in corroboration with the study conducted by (Giltay et al, 1998) which was carried out on smaller population, in which they found significant association between high insulin levels and elevated homocysteine levels in healthy non obese subjects. One study reported elevated homocysteine levels in patients with PCOS and this correlated significantly with fasting insulin (Wijeyaratne et al. 2004). While other did not find any association between PCOS and plasma homocysteine level. In this study, patients were selected on the basis of ultrasound morphology only, not incorporating other components of the syndrome (Sills et al. 2001). An Italian study including 70 PCOS patients with low folate intake and vary high prevalence of the mutated 677T allele, did not show elevated homocysteine concentration in patients with PCOS, as is usually observed in that population (Orio et al. 2003).

Conclusion

In the present study, we examined the association between IR and elevated homocysteine in women with PCOS and found that obesity is not an independent risk factor to increase plasma homocysteine levels in PCOS women. IR was common in PCOS patients and was practically more common in obese PCOS sub groups. In non obese PCOS, the mean plasma homocysteine levels were significantly higher than in obese controls. Thus, we conclude that IR was a significant risk factor for hyperhomocysteinemia. IR could be a part of metabolic syndrome in polycystic ovarian syndrome. Other variables that influence the homocysteine concentration (Vitamin B12 and folate levels) were not examined in this study. However, in this study, sample size is small in metabolic terms, PCOS may possibly be considered a variant of IR.

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