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ASSESSMENT OF HOMOCYSTEINE CONCENTRATION IN INDIVIDUALS DIAGNOSED WITH POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

To compare plasma homocysteine levels in patients with polycystic ovarian syndrome (PCOS) with healthy controls. In this prospective case-control study, homocysteine levels of 200 PCOS women and 200 controls matched by body mass ratio (BMI) were evaluated. The mean level of homocysteine in patients with PCOS was 16.12 ± 0.12 µmol/L and in controls was 11.56 ± 0.04 µmol/L(p=0.030) . Patients with PCOS had a higher risk of hyper homocysteinemia than BMI-matched control women. These data suggest that homocysteine levels are high in the PCOS population. More studies are needed to specifically characterize this relationship.

Keywords: Polycystic Ovary Syndrome, Homocysteine, Blood, Cardiovascular Disease.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) has emerged as a widespread endocrinal disease among young females of fertile age. The pathophysiology of the disease is multifaceted because it grounds numerous manifestations (1–4). It is linked with various correlated diseases such as DM, BP, dyslipidemia, CVD and even cancer from youthful age (4,5). Initial findings suggest that blood biomarkers like white protein, homocysteine, and adiponectin, those are linked to the treatment of CVD, are standard in PCOS (6-9) since levels of hyperhomocysteinemia are observed to be elevated in cases of PCOS than their control counterparts.

Homocysteine is a non-essential amino acid that is produced when methionine is converted into cysteine. It is understood to be metabolized in 2 different all way of trans-sulfuration and re-methylation. Vitamin B is required as a co-factor in this process (5-8). Normal levels of homocysteine vary between 5 and 15 µmol/L.

Hyper-homocysteinemia is categorized into the following forms (10) like mild (around 15 to 30 µmol/L), intermediary (around 30 to 100 µmol/L), and brutal (>100 µmol/L). It's augmentation in blood is universal and ranges between 5-7 % in the universal population.

Hyper-homocysteinemia is an self-governing threat for CAD, neuro-vascular events, and repeated thrombo embolism. This may be due to hereditary defect in the enzyme machinery of homocysteine catabolism like that of methylene tetrahydrofolate reductase (CH3-THFA), cofactors (vitamin), or other spare factors like certain temporary clinical circumstances and medications involving fibrates and nicotinic acid origin (11 -17).

Numerous researchers have studied levels of homocysteine in PCOS, which have higher homocysteine levels in PCOS than normal's (19–24).Very lately, Mancini et al. showed a forthcoming case-control study of 44 subjects with no difference in homocysteine levels between diseased and controls (18). Due to intricate issues of controversial definition of PCOS and lack of literature on other co-factors, results were inevitable to vary. The main idea of our study is to clearly establish a relationship between homocysteine levels in PCOS subjects against control groups. To proceed for the study after ethical clearance, 200 PCOS subjects were included in this forth coming self-funded case-control study.

MATERIALS & METHODS

To achieve our objective, 200 PCOS cases and equal number of Controls were selected and enrolled from the Department of Gynecology of Index Medical College and Hospital, Indore, Madhya Pradesh from a period between 2021 and 2022. All selected subjects were pre-confirmed to have PCOS based on the Darband method of oligomenorrhea (menstrual gap exceeding 42 days) and hyper-androgenism (medically manifested by a Ferriman-Gallaway score of ≤ 8 or alopecia) along with serum testosterone/ free androgen index of 2.36 nmol/liter and/or free index for androgen of 8.98 (29). Hence, not any of the controls met any diagnostic criteria for PCOS as per Rotterdam. All control subjects, on the other hand had regular menstrual cycles and normal androgenemia. It was also take care that none of the members of either group had taken any additional drug (hormonal, metformin, simvastatin and other related drugs) within three months of

the study. A perfect match in body measurement ratio (BMI) was also achieved to determine the incidence of PCOS and controls.

After approval from Institutional Ethical Committee (IEC) of Index Medical College and Research Centre, Indore, Madhya Pradesh, all subjects were selected and then proper consent was acquired. Blood were then collected after an 8 hour overnight fasting, and total homocysteine levels for all selected subjects were assessed using RIA technique.

To establish any relationship between parameters of cases against controls, paired-samples t-test was used. All data were subjected to SPSS (version 22.0) while $p<0.05$ was measured as significance.

RESULTS & DISCUSSION

The age mean of females was seen to be 33.2 ± −5.8 years among cases and 30.6 ± 5.1 years in control group (p=0.06). The mean of BMI was observed to be 33.8 ± 4.1 kg/m² and 23.6 ± 2.0 kg/m² in cases and controls, respectively (Table 1).As per the t-test, there was hardly any significant difference in the BMI of these groups (p=0.1). The mean of homocysteine level in Cases was 16.12 ± 0.12 µmol/L while it was 11.56 ± 0.04 µmol/L in control group

Demographic data is shown in for cases of PCOS along with their controls (Table-I)

Table-I: Demographic data for cases of PCOS and control

Criteria	**PCOS(n=200)**	**CONTROL(n=200)**
Age	33.2 ± 5.8	30.6 ± 5.1
BMI (kg/m²)	33.8 ± 2.1	23.6 ± 2.0
Homocysteine level (mean±standard deviation) micromol/litre	16.12 ± 0.12	11.56 ± 0.04

All values are mean ± standard deviation.

Paired-sample comparison found that PCOS patients had a notably higher risk of hyper-homocysteinemia than BMI-matched control women (Table II).

Table-II Relationship of Hyperhomocysteinemia among PCOS and Controls

* HCY** (µmol/L)

HCY (µmol/L)**	**≥15**	**<15**
PCOS (n=200)	200(100%)	00(00%)
Control(n=200)	00(00%)	200(100%)

Our findings show that blood homocysteine was radically elevated in PCOS than in control group. Our results are steady and similar with an earlier study of Battaglia *et al.* (30).

On around 13 other different studies, our review presented concordance, except to that of Mancini and Yilmaz, (20). Hence Homocysteine is well-established to play a key role in CVD and death.
Homocysteineis understood to have some major metallurgical and prothrombotic properties, like promoting inadequate leukocyte recruitment by stimulating the expression and relaxation of monocytes, chemo-attractant protein-1 and interleukin-8. Homocysteine products can also coalesce LDL-cholesterol to cause foam cells and atherosclerotic plaques in the arteries.
Homocysteine is sought in high levels by physicians, which amplify smooth muscle proliferation and boost collagen manufacture. The prothrombotic role of homocysteine consist of reduction of endothelial cell tissue plasminogen activator binding sites, activation of factors VIIa and V, inhibition of protein C and heparin sulfate, increased fibrinopeptide A and prothrombin fragments 1 and 2, increased blood viscosity, and inhibition of thrombomodulin. Causes of changes include reduction of endothelial anti-thrombotic activity.
Free radicals (ROS) generated at some point in the oxidation of low homocysteine can openly attack endothelial cells. Noticeable platelet aggregation might occur resultant to the pro-aggregator effect of homocysteine. Longperiod of homocysteine exposure with endothelial cells to worsens nitric oxide manufacture. Hyper-homocysteinemia has been associated with myocardial infarction (MI) and recurring cardiac arrest, unfavorable ending post-angioplasty, stenosis of carotid artery, venous thrombosis recurrence, osteoporosis, dementia, and neurological deficits. (31,32).
Homocysteine levels in the PCOS population have been compared with controls by numerous researchers with varying and controversial findings. According to multiple logistic results, age and BMI were non-predictors for hyper-homocysteinemia. Because of the greater rate of hyper-homocysteinemia in PCOS subjects with maximally high fasting insulin levels, we propose that this might be due to the greater occurrence of resistance to insulin in PCOS subjects. (33)
Badawi *et al.* conducted a retrospective study on 90 PCOS subjects using 11μmol/L as the cutoff level for standard homocysteine level, they documented that 41.1% of PCOS cases and 2.9% of control group had higher homocysteine levels, demonstrating the outcome of resistance to insulin due to homocysteine. (23). Kilic-Okman showed significant differences between groups in a study of 29 PCOS patients. (33). In an additional study findings, the instigator observed extensively superior mean of plasma homocysteine levels in insulin-resistant PCOS subjects than in non-insulin-resistant PCOS patients. (34-37).In another report Mancini et al. demonstrated no significant different in homocysteine levels among PCOS women and controls in 44 subjects. In the same study, they also evaluated androgens, fasting blood glucose, insulin level, leptin, fibrinogen, homocysteine, endothelin-1 and air-induced dilation of bronchial artery to establish a relationship between body weight and PCOS.
These investigators also proposed that body weight and PCOS are sovereign boundaries that have effects on endothelial functioning. (18). The need for standardization PCOS and hyper-homocysteinemia, along with the lack of information on supplementary contributing factors such as BMI, fat allotment, and resistance to insulin, may clarify the disparity between our findings and those of other studies.

To border the probable perplexing outcome of different BMIs amid PCOS cases and controls, adjustments were made for this disparity in entire-group assessment. Insulin resistance or its severity was not scrutinized in this objective; hence the liaison among plasma homocysteine levels and insulin resistance cannot be resolute.

It was healthier to bound the possible quantification of different serum homocysteine levels during the menstrual cycle, so all controls and PCOS cases who had regular menstrual cycles had their blood evaluation during the follicular phase of cycle (days 2–5). Nevertheless, our report was not possible due to irregular or absent menstruation in PCOS patients.

CONCLUSION

Although, the accurate risk of hyper-homocysteinemia in PCOS women is mysterious, due to the short of prognostic literature, as well as the small number of studies published in literature, on the unbalanced diagnosis of PCOS in seasoned women. (38-40). Hence, approaching studies with a specific PCOS populace are recommended.

Evaluation for hyper-homocysteinemia up ahead using the contraceptive pill for diagnosis at a youthful age could be valuable. Therapy with controlled diet, physical exercise and minor lifestyle changes might compact with and connected CVD risk, like decrease in overall insulin resistance, regulation in hypertension, and dyslipidemia.

In our future faced case-control study, homocysteine levels of 200 PCOS subjects and 200 body mass ratio (BMI) matched controls by were weighed up. The mean level of homocysteine in PCOS patients was seen to be (16.25±11.94μmol/L) while that of controls were (11.58±3.82μmol/L) ($p=0.002$). Young females with PCOS had been observed to be at a higher potentiated risk category for hyper-homocysteinemia against BMI-matched control women.

These finding simply that homocysteine levels are privileged in the PCOS population. Hence a larger scale of study is needed to specifically characterize the relationship.

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