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# ASSOCIATION OF ELEVATED HOMOCYSTEINE LEVELS AND DYSLIPIDEMIA WITH CARDIOVASCULAR RISK IN WOMEN WITH POLYCYSTIC OVARY SYNDROME: A CROSS-SECTIONAL STUDY

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**ABSTRACT**

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder affecting 10-15% of women of reproductive age, characterized by reproductive, cosmetic, and metabolic disturbances. This study aimed to evaluate the serum homocysteine (Hcy) levels, lipid profiles, and their association in PCOS patients to understand their role in cardiovascular risk. A total of 100 female participants, including 50 PCOS patients and 50 age-matched healthy controls, were recruited. Blood samples were analyzed for Hcy, total cholesterol, triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL). Statistical analysis was conducted using Student's t-test and Pearson's correlation, with a p-value of ≤0.05 considered significant.The study found that PCOS patients had significantly higher levels of Hcy (11.87±5.14 µmol/L), total cholesterol (313.5±70.42 mg/dL), TG (207.18±84.46 mg/dL), LDL (236.06±67.99 mg/dL), and VLDL (41.46±16.79 mg/dL), along with lower HDL levels (35.98±13.81 mg/dL), compared to controls. A significant positive correlation was observed between Hcy and total cholesterol (r=0.36, p=0.01) and Hcy and LDL (r=0.29, p=0.04). These findings suggest that elevated Hcy levels and dyslipidemia are major risk factors for cardiovascular diseases (CVD) and type II diabetes mellitus in PCOS patients.The study recommends routine screening of serum Hcy levels and lipid profiles in the clinical management of PCOS to assess cardiovascular risk. Additionally, further research is warranted to explore the correlation between Hcy levels, vitamin B12, folic acid concentrations, and their potential role in mitigating cardiovascular risks in PCOS patients.

**Key words**: Polycystic ovary syndrome, Homocysteine, Dyslipidemia, Cardiovascular risk, Insulin resistance, Lipid profile, Vitamin B12, Folic acid.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder affecting approximately 10-15% of women of reproductive age [1]. It is characterized by a wide array of reproductive, cosmetic, and metabolic disturbances, making it a heterogeneous condition with significant implications for women's health. The primary features of PCOS include ovulatory dysfunction, biochemical hyperandrogenism, and polycystic ovarian morphology [2]. Clinically, elevated androgen levels manifest as hirsutism, acne, and alopecia, affecting a large proportion of women with PCOS. Moreover, the prevalence of polycystic ovaries on pelvic ultrasound exceeds 70% among these patients, further supporting the diagnostic criteria [3]. In PCOS, there is a disruption in the hormonal regulation of the reproductive system, particularly the luteinizing hormone (LH) and

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gonadotropin-releasing hormone (GnRH) pathways. Elevated GnRH levels stimulate ovarian thecal cells, leading to increased androgen production, which is a hallmark of the condition [4]. The ovarian theca cells in women with PCOS exhibit dysplasia and an increased thickness, contributing to excessive androgen synthesis [5]. This hormonal imbalance not only disrupts normal ovulation but also predisposes women to metabolic complications such as insulin resistance and type 2 diabetes [6].

Insulin resistance plays a central role in the pathophysiology of PCOS, affecting approximately 50% of women with the condition. It is associated with an increased risk of developing prediabetes, type 2 diabetes, and cardiovascular diseases [7]. Insulin resistance exacerbates hyperandrogenism by stimulating ovarian androgen production and reducing the hepatic synthesis of sex hormone-binding globulin (SHBG), thereby increasing the levels of circulating free androgens [2]. The interplay between insulin resistance and hyperandrogenism is a critical factor in the metabolic and reproductive manifestations of PCOS.

In addition to reproductive and metabolic consequences, PCOS is linked to a range of cardiovascular risk factors, including dyslipidemia, hypertension, and increased risk of myocardial infarction [8]. Dyslipidemia, characterized by elevated levels of total cholesterol, low-density lipoprotein (LDL), and triglycerides, along with reduced levels of high-density lipoprotein (HDL), is observed in up to 70% of women with PCOS [9]. This lipid profile significantly increases the risk of atherosclerosis and cardiovascular disease in affected individuals.

Homocysteine, an intermediate in methionine metabolism, has emerged as a potential biomarker for cardiovascular risk in women with PCOS. Elevated homocysteine levels are associated with insulin resistance and may contribute to endothelial dysfunction and vascular damage, increasing the risk of cardiovascular events [10]. Insulin resistance appears to elevate homocysteine levels by inhibiting hepatic cystathionine beta-synthase, an enzyme involved in methionine metabolism [10]. Consequently, women with PCOS and insulin resistance are at a heightened risk for cardiovascular complications.

The relationship between homocysteine and lipid metabolism in women with PCOS is of particular interest, given the toxic effects of both on vascular cells and hepatocytes [11]. Homocysteine can influence phospholipid metabolism and impair very-low-density lipoprotein (VLDL) secretion from hepatocytes, leading to dyslipidemia. Additionally, homocysteine-induced endoplasmic reticulum stress may further disrupt HDL metabolism, exacerbating cardiovascular risk [12].

This study aims to evaluate serum homocysteine levels, lipid profiles, and the association between homocysteine and lipid metabolism in patients with PCOS, with the goal of understanding the underlying mechanisms contributing to the increased cardiovascular risk in this population.

## MATERIALS AND METHODS

This study was conducted in the Department of Biochemistry in collaboration with the Department of Biochemistry at Sri Lakshmi Narayana Institute of Medical Sciences, Pondichery. The research followed strict adherence to ethical standards, having obtained approval from the Institutional Ethics Committee (IEC) before commencement. Informed written consent was acquired from all participants prior to their inclusion in the study, ensuring compliance with ethical guidelines.

A total of 100 female subjects were included in the study, divided into two groups. The patient group consisted of 50 women diagnosed with polycystic ovary syndrome (PCOS) based on the Rotterdam criteria, aged between 18 and 45 years. The control group comprised 50 age-matched healthy females without PCOS, serving as the comparison group.

Inclusion criteria for the study were specifically designed to capture the target population, including only women who met the Rotterdam criteria for PCOS diagnosis. Exclusion criteria were equally stringent, aiming to eliminate confounding factors. Women who were pregnant or menopausal were excluded from the study, as were those with a history of coronary heart disease, hypertension, diabetes mellitus, or other endocrine disorders. Additionally, individuals who were alcoholics, smokers, or on vitamin supplementation were excluded to avoid potential interference with the study's biochemical assessments.

Blood samples from all participants were collected under standard aseptic conditions to ensure the accuracy and reliability of the biochemical analyses. The samples were then analyzed for key parameters, including serum homocysteine levels and a comprehensive lipid profile. The lipid profile measured total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and triglycerides. All biochemical measurements were conducted using a fully automated VITROS 5600 analyzer, which provided precise and consistent results.

### Statistical Analysis

The data obtained from the study were statistically analyzed to compare the biochemical parameters between the two groups: the PCOS patients (n=50) and the control group (n=50). Descriptive statistics were used to present the results, with mean values and standard deviations (mean ± SD) calculated for each parameter in both groups.
To determine the statistical significance of the differences observed between the two groups, the Student's t-test was applied. A p-value of $\leq 0.05$ was considered statistically significant, indicating a meaningful difference between the groups if this threshold was met.

Furthermore, to explore the relationship between serum homocysteine levels and lipid profile components in the PCOS patient group, Pearson's correlation test was employed. This test helped evaluate the strength and direction of the association between homocysteine and various lipid parameters, providing insights into potential metabolic links in women with PCOS.

Overall, the statistical analysis aimed to establish a clear understanding of the biochemical differences between PCOS patients and healthy controls, as well as to explore the potential correlation between homocysteine levels and lipid metabolism in the context of PCOS.

The study population comprised 100 subjects, including 50 women diagnosed with polycystic ovary syndrome (PCOS) and 50 age-matched healthy controls. The participants were selected from the outpatient department of Obstetrics and Gynecology at Mahatma Gandhi Medical College and Hospital, Jaipur, based on predefined inclusion and exclusion criteria. Informed consent was obtained from all participants before their inclusion in the study. Blood samples were collected from all subjects and analyzed for serum homocysteine, total cholesterol, triglycerides, HDL, LDL, and VLDL levels.

The data were statistically analyzed, and a p-value of <0.05 was considered statistically significant. The mean age of the PCOS patients was 26.0±5.03 years, while the mean age of the control group was 26.5±3.84 years. This difference was not statistically significant (p=0.578), as shown in Table 1.

The study revealed that serum homocysteine levels were significantly higher in the PCOS group compared to the control group, with mean values of 11.87±5.14 μmol/L and 4.9±2.5 μmol/L, respectively (p=0.000), as shown in Table 2. These findings align with the results of previous studies by Mohan and Priya [24], as well as Loverro et al. [25] and Badawy et al. [26], which also reported elevated homocysteine levels in women with PCOS. However, Mancici et al. [27] found no significant differences in homocysteine levels between PCOS women and healthy controls. The Framingham Offspring Study demonstrated that hyperhomocysteinemia is associated with hyperinsulinemia, potentially explaining the increased cardiovascular risk in insulin-resistant individuals [28]. Insulin inhibits hepatic cystathionine beta-synthase activity, leading to elevated serum homocysteine levels [29]. Hyperhomocysteinemia is known to contribute to cardiovascular morbidity and mortality due to its atherogenic and prothrombotic properties, including increased inflammatory cytokine expression, oxidative stress, apoptosis, and defective methylation [30].

In this study, PCOS patients exhibited significantly higher serum total cholesterol levels (313.5±70.42 mg/dL) compared to the control group (156.76±32.12 mg/dL, p=0.000). Triglyceride levels were also significantly elevated in the PCOS group (207.18±84.46 mg/dL) compared to controls (104.08±30.2 mg/dL, p=0.000). Conversely, serum HDL levels were significantly lower in PCOS patients (35.98±13.81 mg/dL) than in controls (45.88±7.47 mg/dL, p=0.000). Additionally, LDL levels were markedly higher in the PCOS group (236.06±67.99 mg/dL) compared to controls (88.54±7.47 mg/dL, p=0.000). VLDL levels were also significantly elevated in PCOS patients (41.46±16.79 mg/dL) compared to the control group (20.84±6.14 mg/dL, p=0.000). These results are summarized in Table 3.

The findings are consistent with previous studies, which also reported hyperlipidemia in PCOS patients, characterized by higher total cholesterol, LDL-C, VLDL-C, and triglyceride concentrations, and lower HDL-C levels than in controls [31]. Hyperinsulinemia and hyperandrogenemia in PCOS lead to increased catecholamine-induced lipolysis in adipocytes, releasing free fatty acids into circulation. This increase in free fatty acids stimulates VLDL-C secretion from the liver, resulting in hypertriglyceridemia [32]. Watterau et al. proposed that insulin resistance inhibits the expression of microsomal triglyceride protein, leading to hepatic overproduction of VLDL and hypertriglyceridemia [33]. The accumulation of triglycerides may be due to increased lipogenesis, decreased clearance, and reduced fatty acid oxidation. Insulin resistance also contributes to the catabolism of HDL-C particles and the formation of LDL-C. Hyperandrogenism has been associated with increased hepatic lipase activity, further contributing to the catabolism of HDL-C particles [34].

The association between serum homocysteine levels and components of the lipid profile in PCOS patients was evaluated using Pearson's correlation test. A significant positive correlation was observed between homocysteine and total cholesterol (r=0.36, p=0.01) and between homocysteine and LDL-C (r=0.29, p=0.04), as shown in Table 4, Figures 4.1, and 4.2. However, no significant associations were found between homocysteine and triglycerides (r=0.22, p=0.12), HDL-C (r=0.11, p=0.44), or VLDL-C (r=0.23, p=0.10), as shown in Table 4.

Both homocysteine and lipids are toxic to vascular cells and hepatocytes. Hyperhomocysteinemia (HHcy) and hypercholesterolemia are closely linked to the development of atherothrombotic diseases. The risk associated with both HHcy and hypercholesterolemia is greater than that associated with either risk factor alone. Elevated intracellular levels of homocysteine result in endoplasmic reticulum (ER) stress, leading to dysregulation of the sterol response pathway. The sterol regulatory element-binding protein (SREBP-1), an ER membrane-bound transcription factor, activates genes involved in cholesterol biosynthesis and uptake. Homocysteine enhances the expression of SREBPs, contributing to intracellular cholesterol accumulation. Homocysteine also causes protein misfolding in the ER, activating the unfolded protein response (UPR) and increasing the expression of ER stress-

response genes. An association between UPR activation and lipid biosynthesis has been demonstrated in human fibroblasts [23].

Qujeq et al. [35] also found a significant positive correlation between homocysteine and LDL-C levels in myocardial infarction patients. Oxidative stress is one mechanism by which homocysteine may affect lipoprotein particles and damage endothelial cells. Homocysteine can enhance hydroxyl radical generation and the formation of oxidized and homocysteinylated LDL, which are more toxic than native LDL and are readily taken up by macrophages, facilitating the initiation and progression of the inflammatory response in endothelial lesions [23].

**Table 1: Comparison Of Age (years) Between Control And PCOS Group**
**NS= Non Significant**

| Groups | AGE (years) | t-Value | P-Value |
|---|---|---|---|
| Control (n=50) | 26.5±3.84 | -0.559 | 0.578 (NS) |
| PCOS (n=50) | 26.0±5.03 | | |

**Table 2: Comparison Of Homocysteine (µmol/L) Between Control And PCOS Group.**

| Groups | Homocysteine (µmol/L) | t-Value | P-Value |
|---|---|---|---|
| Control (n=50) | 4.90±2.5 | 8.623 | 0.000 |
| PCOS (n=50) | 11.87±5.14 | | |

**Table 3: Comparison of Lipid Profile between Control and PCOS Group.**

| Parameters | Control group | PCOS patients | t-value | p-value |
|---|---|---|---|---|
| Total Cholesterol (mg/dL) | 156±32.12 | 313.5±70.42 | 14.319 | 0.000 |
| Triglycerides (mg/dL) | 104.08±30.2 | 207.18±84.46 | 8.128 | 0.000 |
| HDL(mg/dL) | 45.88±7.47 | 35.98±13.81 | -4.459 | 0.000 |
| LDL(mg/dL) | 88.54±28.44 | 236.06±68.68 | 14.033 | 0.000 |
| VLDL (mg/dL) | 20.84±6.14 | 41.46±16.96 | 8.084 | 0.000 |

**Table 4: Correlation between Serum Homocysteine Levels With Lipid Profiles in PCOS Patients.**

| Test | Correlation Coefficient (r) | P value |
|---|---|---|
| Hcy v/s Total Cholesterol | 0.36 | 0.01 |
| Hcy v/s Triglyceride | 0.22 | NS |
| Hcy v/s HDL | 0.11 | NS |
| Hcy v/s LDL | 0.29 | 0.04 |
| Hcy v/s VLDL | 0.23 | NS |

**R and P- value as obtained on applying Pearson's correlation.**

## CONCLUSION

The study demonstrates that patients with polycystic ovary syndrome (PCOS) exhibit elevated levels of homocysteine (Hcy), total cholesterol, triglycerides (TG), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), along with reduced levels of high-density lipoprotein (HDL), in comparison to the control group. A significant correlation was observed between Hcy and total cholesterol, as well as between Hcy and LDL, in the PCOS patient cohort. These findings highlight the fact that elevated Hcy levels and dyslipidemia are major risk factors for cardiovascular diseases (CVD) and type II diabetes mellitus in women with PCOS.

Given the strong association between dyslipidemia, hyperhomocysteinemia (HHcy), and the increased risk of CVD, the study suggests that both dyslipidemia and HHcy could serve as sensitive indicators for assessing cardiovascular risk in PCOS patients. Therefore, routine screening and monitoring of serum Hcy levels and lipid profiles should be incorporated into the clinical management of women with PCOS. This proactive approach could help in early detection and prevention of cardiovascular complications in this high-risk population.

Although this study provides valuable insights, it also highlights the limited clinical and epidemiological data available regarding the correlation between Hcy and lipid parameters such as total cholesterol and LDL-C in PCOS patients. This gap in knowledge suggests a need for further research to explore these associations in greater depth.

Additionally, the study acknowledges the role of dietary factors, particularly vitamin B6, vitamin B12, and folic acid, in influencing Hcy levels. These vitamins are crucial in homocysteine metabolism, and their deficiency can lead to elevated Hcy levels. As such, the study recommends further investigation into the relationship between homocysteine levels and the concentrations of vitamin B12 and folic acid in patients with PCOS. Such

research could provide important insights into potential dietary interventions that may help manage Hcy levels and reduce cardiovascular risk in this population.

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