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# Fasting Homocysteine Levels in Pcos

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***Abstract :***
***Background:*** *Poly Cystic Ovarian Syndrome (PCOS) is an endocrine disorder that can significantly batter the quality of reproductive life of women due to insulin resistance. Hyperhomocysteinemia amplifies the insulin resistance and oxidative stress in PCOS. According to the recommendations of the Nutrition Committee of the American Heart Association, fasting plasma Homocysteine should be <10µmol/L, to keep away from all the complications of increased Hcy levels in the future. Hence in the current study, value ≥10µmol/L is considered as hyperhomocysteinemia. Methods: This was a hospital based cross sectional study on 50 PCOS women at SAT hospital, Govt Medical College, Thiruvananthapuram. Height and weight of study population were recorded and body mass index (BMI) was calculated. Biochemical parameters like fasting plasma Homocysteine, Fasting Blood Sugar (FBS) were estimated.*
***Results:*** *Hyperhomocysteinemia was prevalent among 52% of the study population. Mean Homocysteine value obtained in the study was 9.5± 3.6. Homocysteine showed a significant positive correlation with BMI and FBS values.*
***Conclusion:*** *Homocysteine, via its thiolactone derivative play a very decisive role in the pathogenesis of neural tube defects, miscarriages, preeclampsia, gestational diabetes, intra uterine deaths among PCOS women. Therefore plasma Homocysteine has to be considered as a marker for early diagnosis and therapeutic interventions.*
***Keywords:*** *BMI, FBS, Homocysteine, Hyperhomocysteinemia ,PCOS*

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## I. Introduction

Polycystic ovarian syndrome (PCOS) is a highly prevalent hormonal and metabolic disorder among women in their reproductive period. Insulin resistance and oxidative stress are the fundamental factors in the pathophysiology of PCOS. [1, 2, 3] Homocysteine via its thiolactone derivative amplifies the insulin resistance and oxidative stress in PCOS. [4]Homocysteine (Hcy) is an amino acid formed of dietary Methionine metabolism. Some amount of Homocysteine is converted back to Methionine by remethylation, which requires vitamin B-12 and folic acid. Rest of Homocysteine is metabolized to cysteine via the transsulfuration pathway that requires vitamin B-6. The cysteine is either reused for the synthesis of other compounds or is excreted as sulfate. The key enzymes required for Hcy metabolism are Methylene Tetra Hydrofolate Reductase ( MTHFR) and Cystathionine Beta Synthase(CBS). The most common causes of hyperhomocysteinemia are genetic and nutritional. Nutritional deficiencies of vitamin B-6, vitamin B-12 and folic acid can increase the serum Homocysteine levels.[6] Hyperhomocysteinemia has a crucial role in the pathogenesis of coronary artery disease, myocardial infarction, deep vein thrombosis, diabetic nephropathy etc. Elevated Homocysteine levels increase the risk of development of many adverse pregnancy outcomes like placental abruption, intra uterine growth retardation, pre term delivery, low birth weight and intra uterine death of fetus. [7-9] In a famous publication "H factor solution - the best single indicator of whether you are likely to live long or die young" the author concludes the book with the statement- "if your H factor is not below 6, never attempt to become pregnant".

Many prospective and retrospective studies have confirmed the association between PCOS and hyperhomocysteinemia (HHcy). Yarali et al**.** ( 2001), Schachter et al. (2003) E. Badawy et al (2007), [11-13] observed hyperhomocysteinemia among PCOS, but Sills et al. ( 2001), Morgante et al. ( 2002), and Mancini et al.(2009) [14-16]failed to find any difference in the mean Hcy levels between PCOS and healthy women. Homocysteine levels can be reduced by exercise, dietary modifications and adequately supplementing vitamin

B12, folic acid and vitamin B6 as evidenced by many studies. [17, 18] Thus Hhcy is a modifiable condition. In this study attempts were made to investigate the Hcy status and the proportion of hyperhomocysteinemia (Hhcy) in PCOS women and to analyse the prevalence of Hhcy among PCOS women as the incidence of PCOS and PCOS related infertility is high in Kerala. [19, 20]

## II. Methods

The study was a hospital based cross sectional study done on 50 PCOS patients at Sree Avittam Thirunal Hospital, Government Medical College, Thiruvananthapuram. The study was conducted for a period of one year.

### 2.1 Inclusion criteria

The Rotterdam's criteria was used to identify the PCOS patients. Females within 15-35 years identified with any two of the criteria shown below

a) Oligo-ovulation or anovulation manifested as oligomenorrhea or amenorrhea.
b) Hyperandrogenism (clinical evidence of androgen excess-hirsuitism, acne).
c) Polycystic ovaries (as defined on ultrasonography).

### 1.2 Exclusion Criteria

a) Patients who were on folate antagonists/ folic acid
b) Patients who had renal diseases.
c) Patients who were diabetic/hypertensive.
d) Patients who were smokers.

The study was conducted after getting clearance from human ethical committee and review board of the institution. A written informed consent was obtained from all persons included in the study. A detailed history taking and thorough clinical examination of patients were done. History of folic acid intake was enquired. Height and weight of the study subjects were recorded and BMI was calculated from those values. A sonography analysis was performed for the confirmation of PCOS. Fasting blood sample was collected from patients for estimation of Homocysteine levels and blood sugar.

Body mass index was calculated after recording body weight (Kg) and height ($m^2$)

$$BMI = \frac{\text{Weight (kg)}}{\text{Height(square metre)}} \qquad (1)$$

In the current study, BMI is classified as

a) Normal- BMI <27
b) Overweight- BMI 27-30
c) Obese-BMI >30

Hyperhomocysteinemia is defined as an increased fasting plasma Homocysteine levels. Reliable reference intervals for concentrations of Homocysteine in plasma have not yet been established. The normal range of plasma Hcy levels usually accepted are 5-12µmol/L. [21] but still it is a matter of debate. The Nutrition Committee of the American Heart Association proposed <10 µmol/L as a reasonable fasting Hcy value, to avoid all complications of high Homocysteine levels. [22] Accordingly in the current study, value ≥10µmol/L is considered as hyperhomocysteinemia. PCOS patients have a high propensity for diabetes mellitus. According to the latest ADA guidelines, patients in a high-risk group should maintain their fasting blood sugar ≤ 100mg/dl.[23] Hence in the current study, any FBS value >100mg/dl is considered as high blood sugar value.

## III. Statistical Analysis

The data were entered into a personal computer using the package Microsoft excel. For analysis SPSS (Statistical Package for Social Sciences) Window version 16 was used. Continuous variables were expressed as mean ±standard deviation and qualitative data was expressed as percentage. Correlations between variables were done using Pearson correlation test. A 'p' value <0.05 was considered statistically significant.

## IV. Results

**Table: 1 Characteristics of the study group**

| Study Variables | N | Mean | SD |
|---|---|---|---|
| Age (years) | 50 | 26.5 | 4.9 |
| BMI ($kg/m^{2)}$ | 50 | 29.4 | 4.3 |
| Homocysteine | 50 | 9.5 | 3.6 |

| | | | |
|---|---|---|---|
| (µmol/l) | | | |
| FBS (mg/dl) | 50 | 98.4 | 14.5 |

**Table.2 Distribution of patients based on Homocysteine levels**

| Homocysteine | Frequency | Percentage |
|---|---|---|
| ≥10 µmol/l | 26 | 52 |
| <10µmol/l | 24 | 48 |
| Total | 50 | 100 |

The proportion of hyperhomocysteinemia (defined as ≥10µmol/l) was 52% among the study population. Mean Homocysteine in the study was 9.5±3.6 µmol/l.

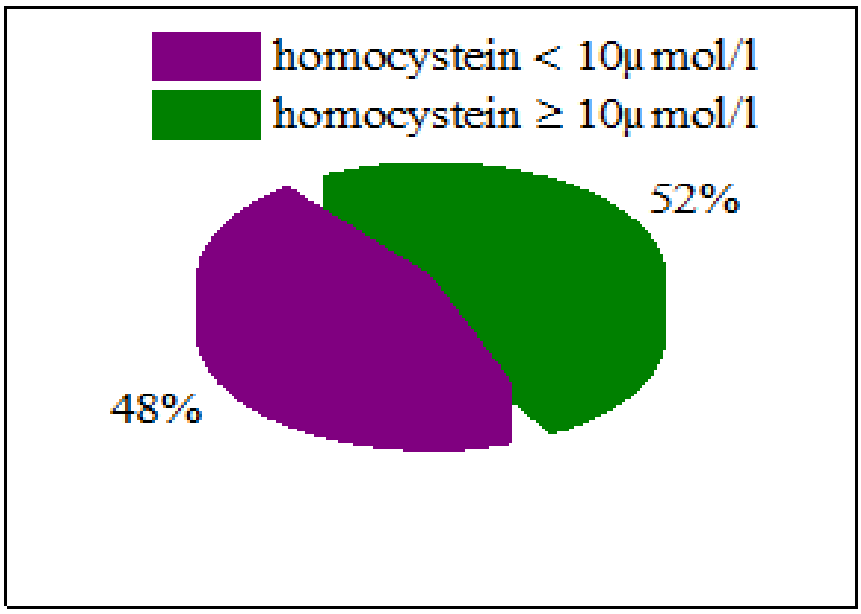


**Fig 1**-Pie diagram showing distribution of patients with Hyperhomocysteinemia

**Table.3 Distribution of patients based on BMI**

| Body mass index(BMI)(kg/m$^2$) | Frequency | Percentage |
|---|---|---|
| Normal (BMI <27) | 10 | 20 |
| Over weight (BMI 27-30) | 20 | 40 |
| Obese (BMI >30) | 20 | 40 |
| Total | 50 | 100 |

Table 1 shows the study parameters and there characteristics of the study group selected. It has been observed that the Obesity is very common among PCOS women. The percentages of both overweight and obese patients were equal (40%) among in study population. Mean BMI of our patients was 29.4 ± 4.3 kg /m$^{2.}$

**Table 4 Distribution of patients based on FBS**

| Fasting blood sugar | Frequency | Percentage |
|---|---|---|
| >100 mg/dl | 20 | 40 |
| ≤100 mg/dl | 30 | 60 |
| Total | 50 | 100 |

The mean FBS was 98.4±14.5mg/dl.

**Table 5 Pearson Correlation between Hcy , BMI and FBS**

| Other parameters in the study | Pearson Correlation (r) | p value |
|---|---|---|
| BMI | 0.380** | 0.006 |
| FBS mg/dl | 0.619** | <0.001 |
| **Correlation | p<0.001– very significant correlation | |

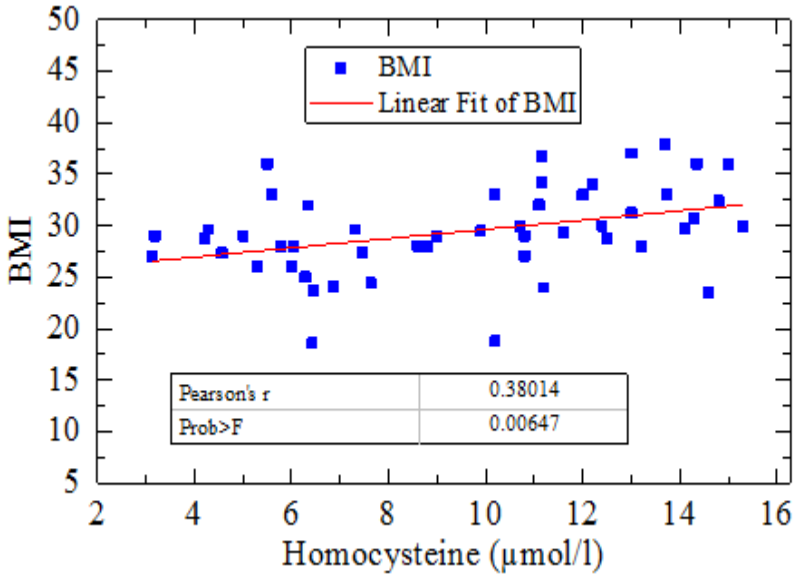


**Fig.2** Correlation between BMI and Homocysteine

Figure 2 shows that there is a significant positive correlation between body mass index and Homocysteine (Pearson Correlation r =.380, p =.006).

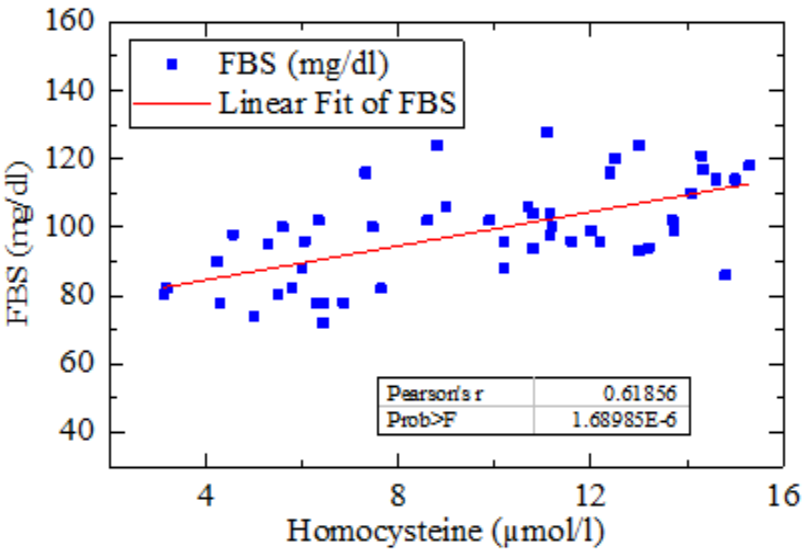


**Fig 3-** Correlation between FBS and Homocysteine

## V. Discussion

In our study 52% of PCOS patients had hyperhomocysteinemia. Insulin resistance, hyperinsulinemia and use of Glyciphage ( Metformin) to improve insulin sensitivity cause Hhcy in PCOS. Insulin and Hcy have the ability to induce each other. Insulin levels have been integrated to increased Hcy levels, as insulin inhibits the 2 key enzymes for Hcy metabolism- MTHFR and hepatic CBS. Hhcy through homocysteine thiolactone, inhibits the tyrosine kinase activity of insulin receptor, affects insulin signaling and induces insulin resistance, resulting in hyperinsulinemia, leading to the accumulation of Hcy in plasma Thus, insulin resistance and hyperhomocysteinemia create a harmful feedback loop, each stimulating the development and propagation of the other and upsurge all complications of PCOS.[25]

Homocysteine, due to the presence of –SH group or sulfhydryl group undergoes auto oxidation and produce reactive oxygen species and aggravates the oxidative stress in PCOS which can badly influence female reproduction by affecting oocyte quality or oocyte function, oocyte penetration and fertilization, causing delayed

conception, improper implantation or loss of an implanted embryo.[26 ]In addition, oxidative stress has an impact on insulin signalling leading to insulin resistance, endothelial dysfunction and atherosclerosis.
The endothelium is susceptible to injury due to Hhcy as it lacks CBS enzyme. Hhcy induced endothelial dysfunction and injury result in reduced vasodilatory capacity, activation of circulating white blood cells and platelets, activation of prothrombotic mechanisms, inhibition of fibrinolytic mechanisms and stimulation of vascular smooth muscle cell proliferation and athero thrombosis. This can lead to pre eclampsia or cause placental insufficiency resulting in intra uterine growth restriction or even death of the fetus during pregnancy. [27, 28]

In our study, 40% of PCOS women were obese and equal percentage of women were overweight. There was a strong positive correlation between Hcy and BMI levels. Similar results were obtained by Gallistl S et al. Zoppini et al, 2008. [29, 30] Obesity in PCOS leads to androgen excess and insulin resistance which induces Hhcy and also increases oxidative stress, favouring the pathogenesis and complications of PCOS. Effects of exercise on plasma total Hcy concentrations in overweight or obese young women with PCOS was examined by Randeva et al. and they concluded that 6 months of brisk walking results in a significant reduction in total plasma Homocysteine concentrations and improve insulin resistance, which in turn help to improve reproductive outcome in these women.[31]

Our study showed a significant positive correlation between Homocysteine and FBS levels. In a study by Nervana et al. among 150 women with anovulatory infertility, a positive association between FBS and Hcy was obtained. [32] As insulin resistance and Hhcy can adversely affect each other there is a high chance of PCOS women becoming frank diabetic in the near future which can produce many future systemic and reproductive comorbidities. The intense treatment of hyperhomocysteinemia in women with polycystic ovary syndrome might improve reproductive outcome and promote protection from the possible cardiovascular risks. This may be achieved by the early screening, lifestyle education, and vitamin B6, B12 and folic acid supplementation. Various steps to lower Hcy levels include [33]

a) Eat more fish and vegetable protein and reduce fatty meat.
b) Consume green leafy vegetables in plenty.
c) Have garlic daily.
d) Don't add excess salt to food.
e) Reduce tea and coffee.
f) Reduce alcohol.
g) Reduce stress.
h) Stop smoking.
i) Supplement a good multi vitamin.
j) A proper well-balanced diet with plenty of water intake.

**Is folic acid safe for everyone?**

In humans, increased folic acid intake leads to elevated blood levels of unmetabolised folic acid. High blood concentrations of folic acid may be related to decreased natural killer cell cytotoxicity and may reduce the response to antifolate drugs used for other diseases. In the elderly, a combination of high folate levels and low vitamin B-12 status may be associated with an increased risk of cognitive impairment and anemia. In pregnant women, excess folic acid increases the risk of insulin resistance and obesity in their children. Folate has a dual effect on cancer; as a protecting agent against cancer initiation, but also as a facilitating agent in the progression and growth of pre-neoplastic cells and subclinical cancers, which are common in the population. This demands folic acid supplementation only to those individuals who require it genuinely, instead of empirical administration; dose should be adjusted according to their Homocysteine levels. The foremost limitation of our study was that we estimated the Homocysteine levels among a small group of PCOS women. Another constraint was the lack of a definite cut off value for Hcy, among women with PCOS. In addition, the diabetic status of our patients was assessed only by fasting blood sugar levels (FBS) and not by oral glucose tolerance test (OGTT), which is the ideal test to detect diabetic PCOS.

## VI. Conclusions

Plasma Hyperhomocysteinemia has been related to various complications and adverse outcomes in polycystic ovarian syndrome. Our study recommends screening of all PCOS women for an elevated Homocysteine level, especially for those who are obese and with a family history of Type 2 DM and CAD. Further studies are required to find out the reference value for Homocysteine in PCOS of our native population. For this, the B vitamin status of our population needs to be explored, since it is the major determinant of serum Homocysteine levels. Also, more studies on MTHFR gene polymorphism and its distribution are needed, so as to elucidate the reasons for the high prevalence of Hyperhomocysteinemia among Indians.

Further research is required in the field of vitamin B supplementation for Hyperhomocysteinemia, to find out the potential or effectiveness of these B vitamins in lowering Homocysteine and thus reducing or improving insulin resistance, hyperlipidemia and raised blood pressure. Advanced research is needed to spot the effects, good and bad, attributable to a high intake of folic acid, from food and dietary supplements. Only then authorities can develop the right strategies for folate supplementation among the general population.

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