Homocysteine As A Noval Risk Factor For Cardiovascular Diseases In Iraqi Females With Polycystic Ovarian Syndrome

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Abstract:

Back ground and objectives: Polycystic ovary syndrome is a common disorder with endocrine and reproductive abnormality which lead to high risk for development of premature atherosclerotic heart disease in reproductive age group. There are many risk factors in women with polycystic ovary syndrome that associated with risk of atherosclerosis. This study was undertaken to evaluate the level of homocysteine as a novel cardiovascular risk marker in polycystic ovarian syndrome women compared to healthy controls.

 Material and Methods: A case-control study done at private clinic in Baghdad in the period from the 1st of August 2015   to the 1st of September 2016. A total of 100 women were enrolled in this study and divided into two groups: (Group 1) fifty diagnosed polycystic ovary syndrome women and fifty (Group 2) healthy age matched controls. Homocysteine, insulin, vitamin B12, folate levels, lipid profile were measured in in both groups.

Results: Homocysteine level was significantly elevated in group 1 compared to group 2 (p<0.001). Also insulin level in group 1 was significantly higher than in group 2 (P=0.001).High density lipoprotein was significantly lower and low density lipoprotein was statistically higher significantly in group1 and the difference was significant (P=0.0001, 0.003 respectively).

Conclusion: Homocysteine was significantly increased in polycystic ovarian syndrome women and can be a marker for early onset of cardiovascular disease in these women.

Index Terms: Homocysteine, Noval risk factors, Cardiovascular diseases, polycystic ovarian syndrome.

I.INTRODUCTION

Polycystic ovarian syndrome is one of the commonest endocrinal diseases that affects about 6-10% of women and characterized by insulin resistance, hyperandrogenimia, obesity, and ovarian dysfunction.[1,2]

The etiology of this syndrome still unknown accurately but hyperandrogenimia appears as a major cause. Nowadays, Polycystic ovarian syndrome is known to have a wide metabolic and cardiovascular aspects.[3]

In polycystic ovary syndrome insulin resistance is a key feature, evidence suggests that insulin resistance plays a central pathological rule in this syndrome. Alteration in lipid profile and cardiovascular disease markers e.g. homocysteine means that polycystic ovarian syndrome may be a risk factor for cardiovascular disease.[4]

Homocysteine is formed by methionine breakdown and may subjected to trans-sulphuration to cystathione and cysteine or remethylation to methionine.[5] Co-factors like folic acid and vitamin B12 are involved in Homocyteine metabolism.[6] Deficiencies of folate and vitamin B12 are known to increase homocysteine level.[7,8]

Many studies have shown that hyperhomocysteinaemia might contribute to the development of cardiovascular complications in polycystic ovary syndrome. It is thought to destroy the vascular endothelium directly and there is an elevated risk of cardiovascular disease and atherosclerogenesis with raised levels of homocysteine.[6,9,10]

Increased homocyteine levels have been positively correlated with insulin levels.[6,11] Insulin thought to affect homocysteine level may be by effects on glomerular filtration rate or alteration of the essential enzymes in homocysteine metabolism. Logically, it is possible to that increased homocysteine level could be associated with insulin resistance and infertility in polycystic ovary syndrome.[3,5]

II. AIM OF THE STUDY

This study was undertaken to measure the level of homocysteine in polycystic ovarian syndrome women as a risk marker for cardiovascular disease as compared to healthy controls.

III. MATERIAL AND METHODS

This study was conducted at private clinic in Baghdad in the period from the 1st of August 2015   to the 1st of September 2016. Hundred women were involved in the study and divided into two groups: **Group (1)** fifty women in reproductive age group with polycystic ovarian syndrome and **Group (2)** fifty normal ovulating women who were matched for age and body mass index (BMI). Rotterdam criteria was used to diagnose women with polycystic ovarian syndrome and is based on clinical recognition at least two of the following:

- Clinical and/or biochemical signs of hyperandrogenemia.

- Oligomenorrhea or amenorrhea.

- Ultrasound findings of polycystic ovaries. Polycystic ovary was diagnosed if 10 subcapsular follicular cysts with diameter of 2–8mm located around a thick ovarian stroma were shown.

Exclusion criteria:
1. Impaired fasting glucose.
2.Diabetes mellitus, hypertension, a family history of coronary artery disease, smoking and acute infections.
3 .Hypopituitarism.
4 .Prolactinoma.
5. Active thyroid disease.
6 .Anorexia nervosa.

7. Hepatic or haematological disease.

8. Congenital adrenal hyperplasia and androgen secreting tumors.

9. Oral contraceptives, glucocorticoids, antiandrogens, ovulation inducing agents, antihypertensive, lipid lowering medication, antidiabetic drugs and any hormones throughout the last six months.

   Informed consent was take from all participant and had undergone body mass index (BMI) estimation by standard equation, the body mass index (BMI) = Weight in kg / height in m², measurement of blood pressure also was done.

   The investigations were done during the early follicular phase (days 1 – 5 of cycle) in women who had menstrual cycles and in days 1-5 of spontaneous or progesterone induced cycles in the amenorrheic polycystic ovarian syndrome patients. All blood samples were obtained in the morning after an overnight fasting.

   Homocysteine serum levels were measured by ST AIA-PACK Homocysteine on the TOSOH AIA System analyzer. Fasting insulin, vitamin B12, folate levels and lipid profile were also measured.

IV. RESULTS

Table 1: The demographic characteristics of the women. There was no statistically significant difference in age, Body mass index (BMI), Systolic and diastolic blood pressure between the two groups.

Characteristic	Group1 n=50	Group2 n=50	p-value
age (Years)	26.7±5.5	27.4±4.5	0.46
BMI (kg/m²)	22.7±2.4	22.4±2.5	0.537
Systolic blood pressure (mm of Hg)	122±21.9	116±7.5	0.07
Diastolic blood pressure (mm of Hg)	75±6.3	73±3.8	0.058

Table 2: Biochemical and hormonal criteria of polycystic ovarian syndrome women an control women. The mean homocysteine and insulin levels were significantly increased in group (1) compared to controls (P<0.001, p=0.001 respectively) while vitamin B12 and folate levels were normal in both groups and the difference was statistically not significant.

Response	Group1 n=50	Group2 n=50	p-value
Homocysteine (μmol/L)	9.6±2.3	5.8±2.1	<0.001*
Vitamin B12 (pg/ml)	351±118	342±105	0.688
Folate(ng/ml)	9.7±2.7	9.3±2.7	0.399
Insulin level(μIu/ml)	9±2.1	5±2.4	0.001*

*: significant

Table 3: Comparison of lipid profile between polycystic ovarian women and control group. High density lipoprotein levels were lower and low density lipoprotein levels were higher significantly in group (1) compared to group (2) (P=0.0001, 0.003 respectively) while cholesterol and triglycerides levels were higher in group 1 but the difference not significant statistically.

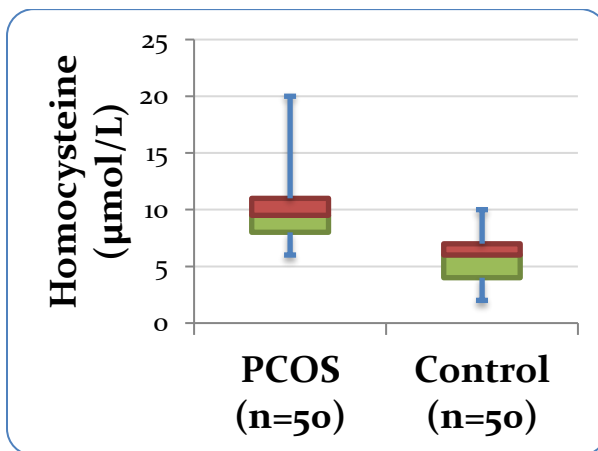| Lipid profile	Group1 n=50	Group2 n=50	p-value
Total cholesterol(mg/dl)	184.2±48.3	179.9±47.1	0.653
Triglycerides(mg/dl)	131±65.9	119±67.9	0.373
HDL (mg/dl)	44.5±7.5	50.3±7.2	0.0001*
LDL (mg/dl)	115±19	103±20.6	0.003*

*:significant

Figure 1: Shows homocysteine levels in polycystic ovarian syndrome women and control women.
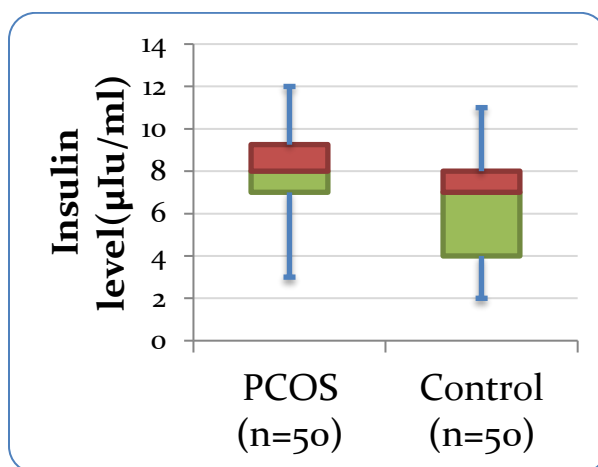

Figure 2:Shows insulin levels in polycystic ovary syndrome women and control women.

V. DISCUSSION

Hyperhomocysteinemia have been found to be important cause for development of ischemic heart disease, preeclampsia and recurrent abortion.[3]Hyperhomocysteinaemia had been known to be related directly with atherosclerosis, thus, elevated homocysteine levels may be beneficial in recognizing a polycystic ovarian syndrome women that are more liable for future development of atherosclerosis and subsequently cardiovascular diseases.[1]

In this study, the demographic characteristics did not differ significantly between the two groups. Previous studies had found that polycystic women have significantly increased plasma homocysteine levels that is not effected by body mass index.[9]

In the present study serum levels of homocysteine were significantly higher in group 1 (P=<0.001) when compared to group 2. The result is similar to reports by many other studies. **S.Lalitha Devi et al**, measured homocysteine levels in women with polycystic ovarian syndrome and found higher levels (P=0.001) when compared to control group.[9] Another studies performed by **Rekha et al.**[3] **M.Schachter et al** [5] showed homocysteine levels were higher significantly in polycystic ovarian syndrome women which was similar to the results of the present study. While another study done by **Orio et al.** found that the homocyteine levels were within normal range in polycystic ovarian syndrome women and similar to the levels measured in controls of this study.[10]

Hyperhomocysteinaemia has been known to induce atherosclerosis by limiting nitric oxide bioavailability and altering the elasticity of blood vessels, activating coagulation system and increasing platelet adhesion.[5,7,9]

In this study both levels of vitamin B12 and folate were normal and the difference was not significant between the two groups (p= 0.688, 0.399 respectively) this in accordance with a study performed by **Orio et al.** who found that no significant difference in both levels between the two groups.[10] **Yilmaz et al** showed the same results that levels of vitamin B12 and folate were the same in polycystic ovarian syndrome women and controls.[12]

Fasting insulin levels were significantly higher in Polycystic group (P <0.01) this agree to previous studies. **Bayraktar et al** did a study showed mean insulin levels in polycystic ovarian syndrome women were increased significantly than controls (P=0.001).[7] and **Valkenburg O et al** found also increased levels of insulin in polycystic women compared to control.[13] Another study done by **Ramalingam et al** agree with this study and found mean insulin levels were increased in polycystic women when compared to control group (P=0.0001).[14] A lot of women with polycystic ovarian syndrome have β-cell dysfunction resulting in decreased insulin response to a high glucose insufficient to lead to insulin resistance. The mechanism that is responsible includes the markedly decreased insulin-induced receptor autophosphorylation that is found in 50% of patients with polycystic ovarian syndrome.[9]

In this study, polycystic ovarian syndrome women had insignificantly higher levels of cholesterol and triglycerides and a significantly lower levels of high density lipoprotein (p=0.0001) and increased low density lipoprotein level (p=0.003). Occurrence and development of lipid disturbance in polycystic ovarian syndrome women is still controversial. These women will be more liable for risk of ischemic heart disease in younger age.[15] Some studies have shown higher lipid disturbance than control. A study performed by **Valkenburg O et al** showed that significantly higher serum Triglycerides, total cholesterol, low density lipoprotein levels and low level of high density lipoprotein (all P values ≤ 0.01).[13] **Atamer et al** study found that serum Triglycerides, total cholesterol, low density lipoprotein levels were not

significantly different from controls while there were lower levels of high density lipoprotein cholesterol in polycystic ovarian syndrome women than in controls and the difference was significant ($P < 0.001$).[1]

VI. CONCLUSION

Early prediction of cardiovascular diseases in polycystic ovarian syndrome women may be beneficial in early prevention of these diseases. Thus Routine screening, appropriate treatment and normalization of this risk factor in these women can play an essential role in early detection and decreasing mortality in these patients through prevention of development of endothelial dysfunction.

VII. RECOMMENDATION

Because of essential diagnostic and management aspects of elevated level of homocysteine in polycystic ovarian syndrome women, it requires more clinical and laboratory testing. Also, managing hyperhomocysteinemia in these patients could increase implantation and decrease abortion rate. Further researches of prospective type can prove the practical aspects of this results regarding increased treatment success.

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