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INSULIN RESISTANCE AND HYPERHOMOCYSTEINEMIA IN PCOS: A PROSPECTIVE STUDY

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ABSTRACT

Insulin resistance, a common feature of polycystic ovarian syndrome (PCOS), is often associated with hyperhomocysteinemia. This prospective study conducted at university-affiliated in vitro fertility clinics aimed to assess homocysteine, insulin, and blood glucose levels in women with and without PCOS. Blood samples were collected from 64 women with PCOS and 50 without, on the third day of their menstrual cycles. Using HOMA-IR and fasting glucose to insulin ratios, insulin resistance levels were compared between the groups. Analysis revealed significantly higher homocysteine levels in PCOS patients compared to controls, particularly among those with insulin resistance (p-value = 0.02). Additionally, fasting insulin and glucose levels were elevated in the insulin-resistant group (p-value = 0.001). These findings suggest a correlation between insulin resistance and hyperhomocysteinemia in PCOS patients, emphasizing the importance of monitoring these metabolic parameters in clinical management.

Key words: Polycystic ovarian syndrome (PCOS), Insulin resistance, Hyperhomocysteinemia, Fertility clinics, Blood glucose levels.

INTRODUCTION

It is common for women in their reproductive years to suffer from polycystic ovarian syndrome (PCOS). As a result, there is ovulation disturbance, hyperandrogenism, infertility, and increased abortion rates. Atherosclerosis, hypertension, dyslipidemia, obesity, hyperinsulinemia, and diabetes are other issues associated with PCOS [1-5]. Homocysteine is an intermediate in the metabolism of methionine which is seen as a consequence of PCOS. An enzymatic defect in this process commonly results in an increased homocysteine plasma level. A number of factors, including enzymes as well as non-enzymatic ones, influence homocysteine levels. Several studies have shown that insulin can affect homocysteine levels due to its inhibitory action on hepatic cystathione beta synthase (6,7). Insulin resistance increases homocysteine levels (8-11). Several studies implicate homocysteine in cardiovascular disease pathogenesis. Heart disease is a condition caused by high levels of homocysteine. 3 times higher mortality is associated with CAD patients who have homocysteine levels greater than 11 mol/L (12, 13). A primary goal of this research is to determine if homocysteine levels are associated with PCOS, and whether insulin resistance is associated with homocysteine levels, both in terms of short-term and long-term outcomes of PCOS treatment.

Methodology

A prospective study on 64 patients were conducted and collaborated on a consensus workshop for the diagnosis of PCOS, according to guidelines. A study and its methodology were approved by the university's ethics committee. All participants received a complete explanation of potential risks, and their informed consent was obtained from them as well. Diabetes or smoking habits were not present in any of the patients. In addition, patients on metformin, folic acid, or phenytoin were not included in the study. A pseudo-random number generator selected 50 other patients with non-ovarian problems from the same unit as the control group.

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A normal ovarian and menstrual cycle was observed, and no PCOS signs or symptoms were present. In order to exclude any known confounding factors, their age and physical activity were matched with those of the PCOS group.

Laboratory tests

Each case in both groups was weighed and measured twice. BMI is calculated by dividing weight (kg) by height squared (m2). A basic plasma level of LH, FSH, and fasting glucose level were measured in the third day of my menstrual cycle (spontaneous or induced by progesterone). Eliza enzyme immunosorbent assays (Calbiotech Inc., CA) were used to measure fasting insulin and homocysteine levels on the same day. BUN, creatinine, and prolactin were measure in addition to thyroid hormone and 17-hydroxyprogesterone. An inspection revealed that their levels were normal. HOMA-IR (Homeostasis model assessment-insulin resistance), which can be calculated by multiplying insulin by glucose, can also be used to determine insulin resistance in addition to total plasma insulin levels (mIU/L) and fasting glucose to insulin ratios (mmol/L). Since it cannot diagnose abnormal glucose levels, and due to its limitations and physiological sensitivity, it is less useful than HOMA-IR. HOMA-IR was used in our study. Due to the rarity of a normal distribution, HOMA-IR is often analyzed on a logarithmic scale (15, 16). A glucose loading test was performed two hours later to measure insulin levels. The experiment was conducted with a threshold of 150 pmol/L. Insulin resistance was classified into three categories based on the upper limit of each index's normal range.

Statistical analysis

Statistics were done with SPSS 16. The results were considered significant if the P-value was less than 0.05. The parametric data groups were compared using the T-test with independent samples. Bivariate correlated items were analyzed using linear regression.

RESULTS

Among the control group, ninety five percent had homocysteine levels below 10.7mol/L, as opposed to five to eleven mol/L considered normal (3). Among the PCOS group, 40.2% (23/64) had homocysteine levels greater than 10.7 mol/L (p0.001), which was deemed hyperhomocysteinemia. A variety of indices were used in our study to measure insulin resistance. A normal control group was used as the upper limit for each variable. Based on a A glucose-to-insulin ratio of 0.33 and a HOMA-IR of 2.0 of 0.57, we determined a fasting insulin level of 20 mIU/L. Among patients with insulin resistance, 35.94%, 48.44%, and 57.81% also had the condition. After glucose loading, 45.31 percent of individuals with insulin resistance had high insulin levels. There is a significant difference between these results and those of the control group (all groups, p = 0.001). In the rest of the study, we used HOMA-IR. In PCOS, insulin resistance (IR) and non-insulin resistance (NIR) were determined by their log HOMA-IR. There was a significant difference between the NIR and IR groups in homocysteine levels (p-value=0.02), fasting insulin levels (p=0.001), and glucose levels (p=0.001). However, Log HOMA-IR and BMI did not show a significant correlation (p=0.18). As compared to NIR-PCOS, 48.52% (18/37) of IR-PCOS patients had higher homocysteine levels than 18.52% (5/27) of NIR-PCOS patients (IR-PCOS homocysteine levels 10.6 x 5.4, p = 0.002). Comparing PCOS patients with the control group, higher BMI had no significant effect on homocysteine level or insulin resistance (p=0.06). There were similar results between the PCOS and BMI care groups in terms of homocysteine and log HOMA-IR levels as well (p-values are 0.4 and 0.9), as well as in terms of homocysteine and log HOMA-IR measurements in the BMI care group. Among those with PCOS, 12.88% had a BMI above 27 kg/m2. PCOS patients had a significantly elevated LH/FSH ratio compared to the control group Obesity, insulin resistance, or neither (p0.001). A p-value of 0.001 indicates that age is related to BMI only (no other variables were involved). Among all insulin resistance indices, homocysteine levels were correlated. Insulin level is correlated strongly with fasting insulin levels, glucose/insulin is -0.3, log HOMA-IR is 0.3, ins2hr R=0.37, P=0.002, and log HOMA-IR is 0.3.

Table 1: Detailed clinical and biochemical information on every patient.

	50 controls (N=50)	UNIX (N=64)	Value of p
Number of years (in years)	21.1±3.3	31.20±9.5	0.23
The body mass index (kg/m2)	22.1±0.12	22.3±3.9	<0.08
(mol/l) Homocysteine	6.8±1.95	10.7±7.6	<0.001
The level of insulin in the blood (mIU/l)	10.8±4.5	18.7±8.5	<0.001
HCG/FSH	0.9±0.3	1.77±2	<0.001
Relative insulin/glucose levels	0.22±0.13	0.32±0.31	<0.001
Record of HOMA-IR	0.96±0.21	0.58±0.41	<0.001

Table 2: Insulin resistance and PCOS patient groups

	Number of patients	Glucosamine	Keeping a fast	Insulin fasting	Diabetes/Insulin	Body Mass Index
POC-NIR	33	8.6±5.8	83.9±36	11.2±2.5	0.44±0.3	25.3±2.6
IR-PCOS	66	12.6±5.7	97.5±11.5	24.4±6.9	0.23±0.06	24.2±4.7
Value of p		0.22	<0.021	<0.002	<0.001	0.44

DISCUSSION

Compared with the control group, the PCOS group had significantly higher homocysteine levels and higher insulin resistance. A group of PCOS patients with diabetes-resistant and non-diabetic conditions was established. Insulin resistance and homocysteine levels were significantly correlated in the study. Recently, researchers have investigated the local and systemic effects of insulin resistance. Hyperhomocysteinemia has been associated with several phenotypes of insulin resistance syndrome (17). Insulin resistance occurs more frequently in fertile women who have elevated homocysteine levels. A study (18) found that pregnant women with preeclampsia have hyperhomocysteinemia, which causes insulin resistance. There was a greater correlation between preeclampsia and these factors than among control subjects. These individuals also have high homocysteine levels. On average, homocysteine levels were higher in the IR group than in the NIR group ($p = 0.026$). In insulin resistance, hyperhomocysteinemia can partially be explained, but not entirely. It is possible that PCOS is caused by steroidal sex hormones or hyperandrogenism relative to other hormones. Persons with PCOS have elevated levels of plasma homocysteine and insulin resistance, according to Bayraktar et al. Patients with congenital adrenal hyperplasia do not exhibit such a relationship (20). An insulin study found no correlation between polycystic ovaries and insulin levels. The study used only one ultrasound feature. PCOS criteria other than those listed above were not taken into account. They may have reached contradictory conclusions for a reason. Hyperhomocysteinemia in PCOS may not only be caused by insulin resistance, according to a study. The results may have been influenced by the smaller sample size (n=29) (22). In healthy individuals, insulin resistance is reversed by high homocysteine levels (23). PCOS, insulin resistance, and hyperhomocysteinaemia may be defined differently among population groups due to these differences in definitions. A number of studies have linked homocysteine to cardiovascular disease (12, 13). Although LH imbalances and hyperandrogenism may have been corrected in PCOS, loss of implantation and early pregnancy still occurs. Due to its effects on vascular structure, hyperhomocysteinemia could cause all of these conditions. Hypertension, nephropathy, and dyslipidemia are all associated with insulin resistance. Hyperhomocysteinemia aggravates metabolic syndrome symptoms. It is possible to consider PCOS at an early stage of its development as a form of insulin resistance. Several factors, however, influence blood homocysteine levels. The other metabolic complications should be considered if PCOS is diagnosed. It is essential to treat gynecological disorders and infertility together. Homocysteine plasma levels should be studied in greater depth in insulin sensitizers. According to other studies, clinical assessment of hyperhomocysteineemia complications is necessary for managing PCOS. PCOS morbidity may be reduced by treating hyperhomocysteinaemia actively. Patients with PCOS may benefit from prospective studies of these treatments.

CONCLUSION

Based on the results and implications of this study, it can be concluded that elevated plasma homocysteine levels are significantly associated with insulin resistance in patients with polycystic ovarian syndrome (PCOS). The findings suggest that hypohomocysteinemia may contribute to the development or exacerbation of insulin resistance in PCOS. Further research is needed to elucidate the underlying mechanisms linking homocysteine metabolism and insulin sensitivity in order to identify potential therapeutic targets for managing insulin resistance in PCOS.

REFERENCE

1. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev* 1997, 18, 774-800.
2. Gennarelli G, Holte J, Berglund L, Berne C, Massobrio M, Lithell H. *et al*., Prediction models for insulin resistance in the polycystic ovary syndrome. *Hum Reprod*. 2000, 15, 2098- 2102.
3. Schachter M, Raziel A, Friedler S, Strassburger D, Bern O, Ron-El R. *et al.,* Insulin resistance in patients with polycystic ovary syndrome is associated with elevated plasma homocysteine. *Hum Reprod* 2003, 18, 721-727.
4. Talbott E, Guzick D, Clerici A, Berga S, Detre K, Weimer K, *et al.* Coronary heart disease risk factors in women with polycystic ovary syndrome. *Arterioscler Thromb Vasc Biol* 1995, 15, 821-826.
5. Robinson S, Henderson AD, Gelding SV, Kiddy D, Niththyananthan R, Bush A, *et al*. Dyslipidaemia is associated with insulin resistance in women with polycystic ovaries. Clin Endocrinol (Oxf) 1996, 44, 277- 284.

6. Giltay EJ, Hoogeveen EK, Elbers JM, Gooren LJ, Asscheman H, Stehouwer CD. *et al.,* Effects of sex steroids on plasma total homocysteine levels: a study in transsexual males and females. *J Clin Endocrinol Metab* 83, 1998, 550-553.
7. McCarty MF. Increased homocysteine associated with smoking, chronic inflammation, and aging may reflect acute-phase induction of pyridoxal phosphatase activity. *Med Hypotheses* 55, 2000, 289-293.
8. Nygard O, Refsum H, Ueland PM, Vollset SE. *et al*., Major lifestyle determinants of plasma total homocysteine distribution: the Hordaland Homocysteine Study. *Am J Clin Nutr* 1998, 67, 263-270.
9. House JD, Jacobs RL, Stead LM, Brosnan ME, Brosnan JT. *et al.,* Regulation of homocysteine metabolism. Adv Enzyme Regul 1999, 39, 69-91.
10. McCarty MF. Insulin secretion as a potential determinant of homocysteine levels. *Med Hypotheses* 55, 2000, 454- 455.
11. Bar-On H, Kidron M, Friedlander Y, Ben-Yehuda A, Selhub J, Rosenberg IH, *et al.* Plasma total homocysteine levels in subjects with hyper insulinemia. *J Intern Med* 247, 2000, 287-294.
12. Karaer A, Cavkaytar S, Mert I, Buyukkagnici U, Batioglu S. *et al.,* Cardiovascular risk factors in polycystic ovary syndrome. *J Obstet Gynaecol* 2010, 30, 387-392.
13. Mohamadin AM, Habib FA, Al-Saggaf AA. *et al*., Cardiovascular disease markers in women with polycystic ovary syndrome with emphasis on asymmetric dimethylarginine and homocysteine. *Ann Saudi Med* 2010, 30, 278-283.
14. Broekmans FJ, Knauff EA, Valkenburg O, Laven JS, Eijkemans MJ, Fauser BC. *et al.,* PCOS according to the Rotterdam consensus criteria: Change in prevalence among WHO-II anovulation and association with metabolic factors. *BJOG* 2006; 113, 1210-1217.
15. Quon MJ. *et al*., Limitations of the fasting glucose to insulin ratio as an index of insulin sensitivity. *J Clin Endocrinol Metab* 2001, 86, 4615-4617.
16. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 27, 2004, 1487-1495.
17. Meigs JB, Jacques PF, Selhub J, Singer DE, Nathan DM, Rifai N, *et al;* Framingham Offspring Study. Fasting plasma homocysteine levels in the insulin resistance syndrome: the Framingham offspring study. *Diabetes Care* 24, 2001, 1403-1410.
18. Laivuori H, Kaaja R, Turpeinen U, Viinikka L, Ylikorkala O. *et al.,* Plasma homocysteine levels elevated and inversely related to insulin sensitivity in preeclampsia. *Obstet Gynecol* 93, 1999, 489-493.
19. Badawy A, State O, El Gawad SSh, El Aziz OA. *et al*., Plasma homocysteine and polycystic ovary syndrome: the missed link. *Eur J Obstet Gynecol Reprod Biol* 2007, 131, 68-72.
20. Bayraktar F, Dereli D, Ozgen AG, Yilmaz C. *et al.,* Plasma homocysteine levels in polycystic ovary syndrome and congenital adrenal hyperplasia. *Endocr J* 2004; 51: 601- 608.
21. Sills ES, Genton MG, Perloe M, Schattman GL, Bralley JA, Tucker MJ. *et al*., Plasma homocysteine, fasting insulin, and androgen patterns among women with polycystic ovaries and infertility. *J Obstet Gynaecol Res*, 27, 2001, 163-168.
22. Kilic-Okman T, Guldiken S, Kucuk M. *et al.,*Relationship between homocysteine and insulin resistance in women with polycystic ovary syndrome. *Endocr J* 51, 2004, 505- 508.
23. Rosolová H, Simon J, Mayer O Jr, Racek J, Dierzé T, Jacobsen DW. *et al.,* Unexpected inverse relationship between insulin resistance and serum homocysteine in healthy subjects. Physiol Res 51, 2002, 93-98.