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Effect of Metformin on Homocysteine Levels in Lean PCOS Patients

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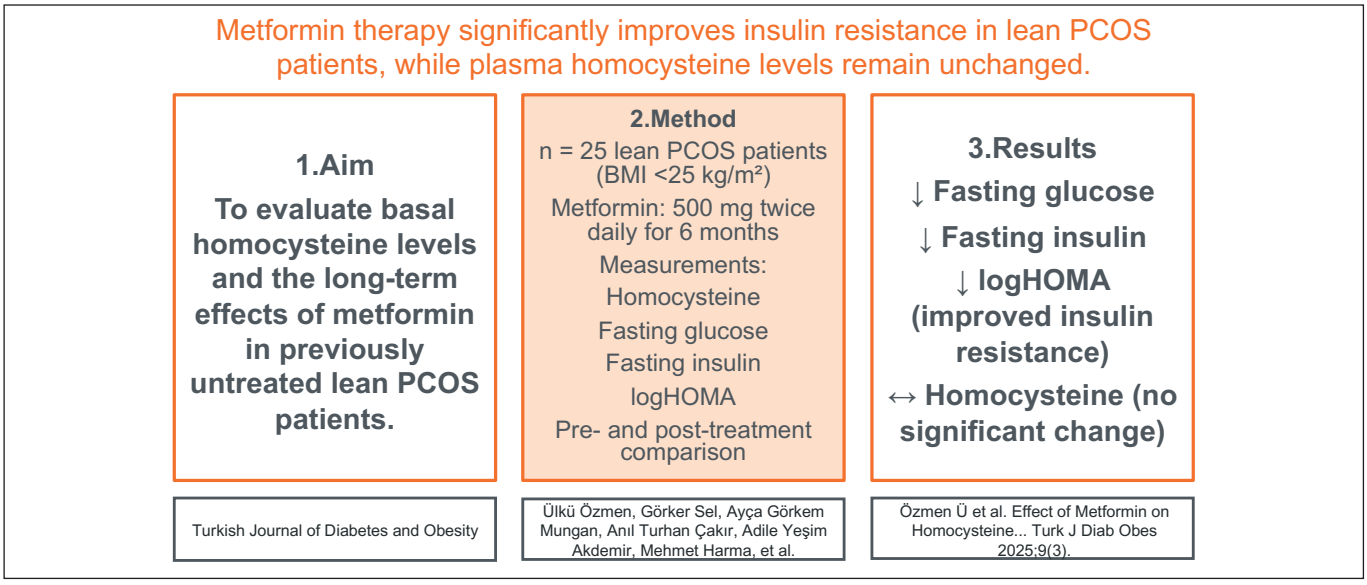
GRAPHICAL ABSTRACT



ABSTRACT

Aim: Increased levels of homocysteine have been considered as a significant risk factor for cardiovascular disease. Elevated levels have been demonstrated in polycystic ovary syndrome (PCOS) patients, and have been found to be associated with insulin resistance in PCOS. This study aimed to determine the basal homocysteine levels and insulin sensitivity status in previously untreated lean PCOS patients and to evaluate the effect of metformin as a long term treatment modality.

Material and Methods: Twenty-five lean (BMI <25kg/m2) patients with PCOS were recruited to the study. Metformin 500mg orally twice daily was administered for 6 months. Before and after initiation of the study, after 12h fasting, homocysteine, insulin, glucose, FSH, LH, estradiol, progesterone, prolactin, free testosterone levels were measured and 75g OGTTs were performed. Normality was assessed with the Shapiro-Wilk test. Paired Student's t-test or Wilcoxon signed-rank test was used as appropriate, categorical variables were analyzed with the McNemar test, and correlations were evaluated with Spearman analysis ($p<0.05$).

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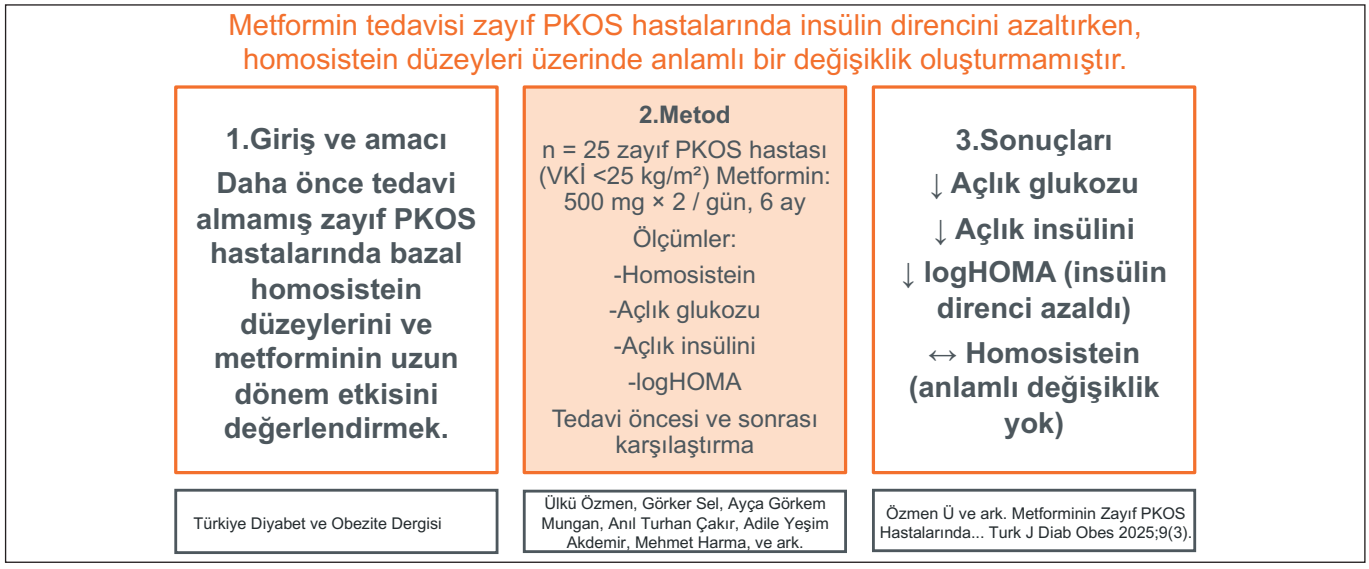
Results: Pre-treatment (pre) and posttreatment (post) homocysteine levels were within normal levels (median (min-max)) (pre:6.1µmol/L (1.2-25.3), post: 6.2µmol/L (2.0-20.0), p=0.59). Metformin treatment significantly reduced fasting blood glucose (pre:93.7±9.6mg/dL; post:84.8±8.8mg/dL, p=0.003), fasting insulin (pre: 18.1±9.5µU/mL; post: 12.3±5.2µU/mL, p=0.02), and logHOMA (pre: 0.59±0.16, post: 0.37±0.17, p<0.001) values.

Conclusion: Homocystein levels were within normal range in previously untreated lean PCOS patients. Insulin resistance was present in significant proportion of patients which also decreased after treatment. However, metformin treatment had no significant effect on homocysteine values.

Keywords: *Homocysteine, Insulin resistance, Metformin, PCOS*

Metforminin Zayıf PKOS Hastalarında Homosistein Düzeyleri Üzerindeki Etkisi

GRAFİKSEL ÖZET



ÖZ

Amaç: Homosistein düzeylerindeki artış kardiyovasküler hastalıklar için önemli bir risk faktörü olarak kabul edilmektedir. Polikistik over sendromu (PKOS) hastalarında yüksek düzeyler gösterilmiş ve PKOS'ta insülin direnci ile ilişkili olduğu bildirilmiştir. Bu çalışmanın amacı, daha önce tedavi görmemiş zayıf PKOS hastalarında bazal homosistein düzeylerini ve insülin duyarlılığını belirlemek ve metforminin uzun süreli bir tedavi yöntemi olarak etkisini değerlendirmektir.

Gereç ve Yöntemler: Yirmi beş zayıf (VKİ <25 kg/m²) PKOS hastası çalışmaya dahil edildi. Metformin 500 mg oral yoldan günde iki kez 6 ay boyunca uygulandı. Çalışmanın başlangıcında ve 6. ayda, 12 saatlik açlık sonrası homosistein, insülin, glikoz, FSH, LH, östradiol, progesteron, prolaktin ve serbest testosteron düzeyleri ölçüldü ve 75 g OGTT yapıldı. Verilerin normal dağılıma uygunluğu Shapiro-Wilk testi ile değerlendirildi. Parametrik veriler eşleştirilmiş Student t-testi, nonparametrik veriler Wilcoxon işaretli sıralar testi ile analiz edildi. Kategorik değişkenler McNemar testi ile karşılaştırıldı; korelasyon analizlerinde Spearman testi kullanıldı (p<0,05 anlamlı kabul edildi).

Bulgular: Tedavi öncesi ve sonrası homosistein düzeyleri normal seviyelerdeydi (medyan (min-maks)) (öncesi: 6,1 µmol/L (1,2-25,3), sonrası: 6,2 µmol/L (2,0-20,0), p=0,59). Metformin tedavisi açlık kan şekeri (öncesi: 93,7 ± 9,6 mg/dL; sonrası: 84,8 ± 8,8 mg/dL, p=0,003), açlık insülin (öncesi: 18,1 ± 9,5 µU/mL; sonrası: 12,3 ± 5,2 µU/mL, p=0,02) ve logHOMA (öncesi: 0,59 ± 0,16, sonrası: 0,37 ± 0,17, p<0,001) değerlerini anlamlı şekilde azalttı.

Sonuç: Daha önce tedavi görmemiş zayıf PKOS hastalarında homosistein düzeyleri normal sınırlardaydı. Hastaların önemli bir kısmında insülin direnci mevcuttu ve metformin tedavisi sonrasında bu direnç belirgin olarak azaldı. Ancak metformin tedavisinin homosistein düzeyleri üzerinde anlamlı bir etkisi olmadı.

Anahtar Sözcükler: *Homosistein, Polikistik over sendromu, Metformin, İnsulin direnci*

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder, affecting approximately 6-10% of women of reproductive age (1). It is regarded as a multifaceted metabolic condition in which insulin resistance plays a central role (2). Hyperinsulinemia is secondary to insulin resistance that is seen both obese and non-obese women (3). The underlying mechanism responsible for insulin resistance in PCOS has not been fully elucidated. Nonetheless, insulin is thought to be a key driver in PCOS pathophysiology, in part through stimulation of cytochrome P450c17α activity, which can enhance androgen synthesis in both ovarian theca cells and the adrenal cortex. In addition, insulin may act at the hepatic level to suppress the production of sex hormone-binding globulin (SHBG), thereby increasing bioavailable androgens (4,5). Long-term sequelae linked to insulin resistance include impaired glucose tolerance and progression to type 2 diabetes mellitus, dyslipidaemia (typically reduced HDL cholesterol and elevated triglycerides), and an increased risk of cardiovascular disease (6,7). Therefore treatments directed towards insulin resistance (insulin sensitizing drugs) gaining acceptance for acute (subfertility) and chronic treatment of PCOS (8,9). However, long term effects of metformin on cardiovascular risks are still unknown. Additionally, there is no proven surrogate marker for cardiovascular disease in PCOS patients. Therefore, unlike subfertility evaluation, modification of cardiovascular risk factors is difficult for studies that assess the success of long term metformin treatment. Also data regarding the treatment of subgroups of patients (obese and lean) is insufficient (9).

Increased homocysteine concentrations have deleterious effects on the vascular endothelium. Elevated levels can promote endothelial dysfunction and may accelerate atherosclerotic processes, independent of conventional cardiovascular risk factors, in both diabetic and non-diabetic individuals (10,11). In general population as a surrogate marker of cardiovascular disease risk, lowering plasma homocysteine improves endothelial function in individuals with coronary artery disease (12) and decreases the incidence of major cardiac events (13). Elevated homocysteine levels associated with insulin resistance in PCOS patients (14).

In this study we aimed to assess the basal levels of homocysteine levels and parameters related with insulin resistance (fasting glucose and insulin levels, lipid profile, and insulin sensitivity indices) previously untreated lean PCOS patients. We also aimed to determine the effects of metformin on these parameters as a long-term therapeutic option.

MATERIAL and METHODS

Patient selection

During the study period of 2004-2005, twenty-five patients with PCOS who attended the outpatient clinics of the Gynaecology Unit of the Zonguldak Karaelmas University Hospital were recruited to the study. Written informed consent was obtained from all participants, and the study protocol was approved by the local ethics committee (2003/03-3. 03.04.2003).

The diagnosis of PCOS was established by the presence of any two of the following: (i) polycystic ovaries; (ii) oligo-/anovulation; and/or (iii) clinical or biochemical evidence of hyperandrogenism (15). Polycystic ovarian morphology on transvaginal ultrasound was defined as the presence of at least 12 follicles in each ovary measuring 2-9 mm in diameter and/or an increased ovarian volume (≥10 mL) (16). Patients with Cushing disease, hypothyroidism, hyperthyroidism, congenital adrenal hyperplasia, prolactinoma, were excluded from the study. Body mass index (BMI), calculated as weight (kg) divided by height squared (m^2), was used as an indicator of overall adiposity.

Study design and intervention

The study was conducted as a prospective pre-post clinical trial. Participants received oral metformin at a dose of 500 mg twice daily for six months. Blood samples were obtained after a 12-hour fast at baseline (before treatment initiation) and again at the end of the 6-month treatment period. Blood for fasting levels of homocysteine, insulin, glucose, FSH, LH, oestradiol, progesterone, prolactin, free testosterone was drawn after at least 20 minutes of rest to prevent excessive hormone secretion. After taking blood samples, a 75g OGTT was performed with insulin and glucose measurements at 30 min intervals for 2 hr. Following these measurements all blood samples were centrifuged and stored at -40° until the completion of the study after when all the collected samples were studied together for the parameters other than glucose and insulin. Serum fasting homocysteine, FSH, LH, oestradiol, progesterone, prolactin, free testosterone were measured at the end of the study. All participants were advised to continue their habitual diet throughout the study period.

Assays

Plasma glucose and lipid parameters (total cholesterol, triglycerides, HDL, LDL, VLDL, and lipoprotein(a)), along with liver enzymes (AST, ALT), were quantified using a colorimetric method on an automated analyzer (Roche Cobas Integra 800; Mannheim, Germany). Serum insulin and hormonal assays—including progesterone, free testosterone, FSH, LH, estradiol (E2), prolactin, cortisol, and DHEAS—

were determined by electrochemiluminescence on an immunoassay platform (Roche Elecsys 2010; Mannheim, Germany). Plasma homocysteine levels were measured using The Axis enzyme Immunoassay kit (Oslo, Norway) on an ELISA analyzer (Pasteur Diagnostics LP 400, French). Free Testosterone level was measured using the competitive binding immunoassay technique on an ELISA analyser (Pasteur Diagnostics LP 400, French).

Measurements and calculations

The glucose-insulin (GI) ratio was determined by dividing fasting plasma glucose (mmol/L) by fasting insulin (μU/mL). Insulin resistance was estimated using the HOMA-IR index, calculated as: fasting glucose (mmol/L) × fasting insulin (μU/mL) / 22.5 (17). The Quantitative Insulin Sensitivity Check Index (QUICKI) was computed using the formula: QUICKI = 1 / (log(fasting insulin (μU/mL)) + log(fasting glucose (mg/dL))) (18). Insulin sensitivity during the OGTT was estimated using the ISI-OGTT (Matsuda index) as described by Matsuda et al.:

ISI-OGTT = 10,000 / √(fasting glucose (mg/dL) × fasting insulin (μU/mL) × mean glucose during OGTT × mean insulin during OGTT) (19).

Sample size determination and statistical analyses

Sample size determination was based on the expected difference in homocysteine levels before and after treatment. A sample size of 20 patients (40 measurements) was calculated to be sufficient to detect at least a 2 μmol/L difference between two measurements, with α (type I error) set at 0.05 and 80% power, using the G*Power 3.1 software. The final sample of 25 patients therefore exceeded the minimum requirement. All patients were followed prospectively by a custom form for recording variables and contact information. Data were recorded in an SPSS database for analysis (SPSS for Windows 11.5, SPSS Inc., Chicago, IL, USA). Normal distribution of continuous variables was assessed using the Shapiro-Wilk test. Variable pairs recorded before and after treatment were compared with Student's t test for paired samples or the Wilcoxon signed-rank test for parametric and nonparametric data, respectively. The McNemar test was used to compare paired categorical data (e.g. the proportion of insulin resistant patients before and after treatment). Results were expressed as mean ± standard deviation (SD) for parametric data, median (minimum-maximum) for nonparametric data, and count (%) for categorical data. Correlations between homocysteine, insulin, logHOMA and BMI were evaluated using the Spearman correlation test. In all calculations, statistical significance was defined as $p<0.05$.

Table 1. Baseline descriptive characteristics of lean PCOS patients (n = 25)

Characteristics	Results (n=25)
Age (years±SD)	27.4 ± 6.1
BMI (kg/m²±SD)	23.5 ± 0.9
FSH (mIU/L±SD)	5.3 ± 1.4
LH (mIU/L±SD)	10.6 ± 4.8
DHEAS (μg/dL±SD)	320.5 ± 180.2
Free testosterone (pg/mL±SD)	3.2 (2.1-27.2)
Homocysteine (μmol/L±SD)	6.1 (1.2-25.3)
Fasting glucose (mg/dL±SD)	93.7 ± 9.6
Fasting insulin (μU/mL±SD)	18.1 ± 9.5
logHOMA±SD	0.59 ± 0.16
QUICKI±SD	0.31 ± 0.02
ISIOGTT±SD	3.54 (1.56-7.23)
Insulin resistance (logHOMA ≥ 0.5), n (%)	17 (68.0%)

BMI: Body mass index; **FSH:** Follicle-stimulating hormone; **LH:** Luteinizing hormone; **DHEAS:** Dehydroepiandrosterone sulfate; **GI ratio:** Glucose/insulin ratio; **HOMA-IR:** Homeostasis Model Assessment for Insulin Resistance; **QUICKI:** Quantitative Insulin Sensitivity Check Index; **ISIOGTT:** Insulin Sensitivity Index derived from Oral Glucose Tolerance Test; **PCOS:** Polycystic Ovary Syndrome.

RESULTS

Mean (±SD) age and BMI values of patients were 27.4±6.1 years and 23.50 ± 0.9 kg/m², respectively. Baseline descriptive characteristics of lean PCOS patients are summarized in Table 1.

Homocysteine levels

Pre-treatment (6.0 (1.2-25.3) mmol/L) and posttreatment (6.2 (2.0-20.0) mmol/L) homocysteine levels were within normal range (5-11 mmol/mL) (14) (Figure 1). No statisti-

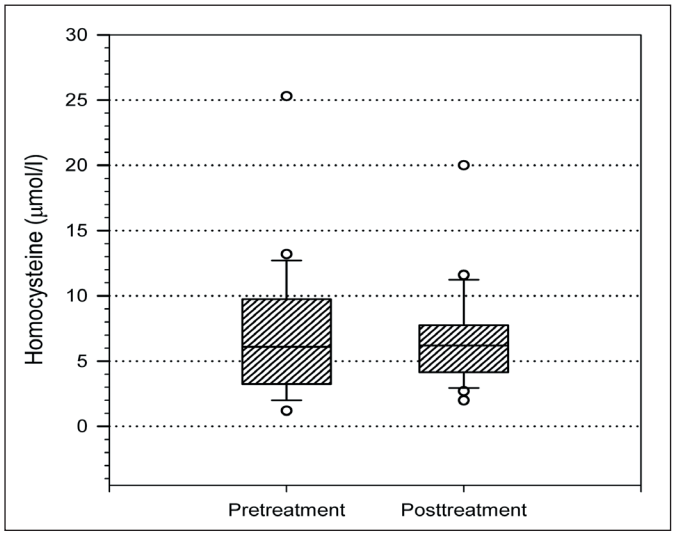


Figure 1: Pre-, posttreatment homocysteine levels (p=0.59)

Table 2. Subgroup analysis of basal homocysteine levels according to insulin resistance status in lean PCOS patients

Homocysteine levels	NIR†	‡IR	P
Pretreatment homocysteine (mmol/L)	6.0 (1.2-13.2)	6.1 (3.4-25.3)	0.71
Posttreatment homocysteine (mmol/L)	6.1 (2.0-7.7)	6.2 (2.7-20.0)	0.79

Note: Values are expressed as median (minimum-maximum)
† NIR: Non-insulin resistant
‡IR: Insulin resistant

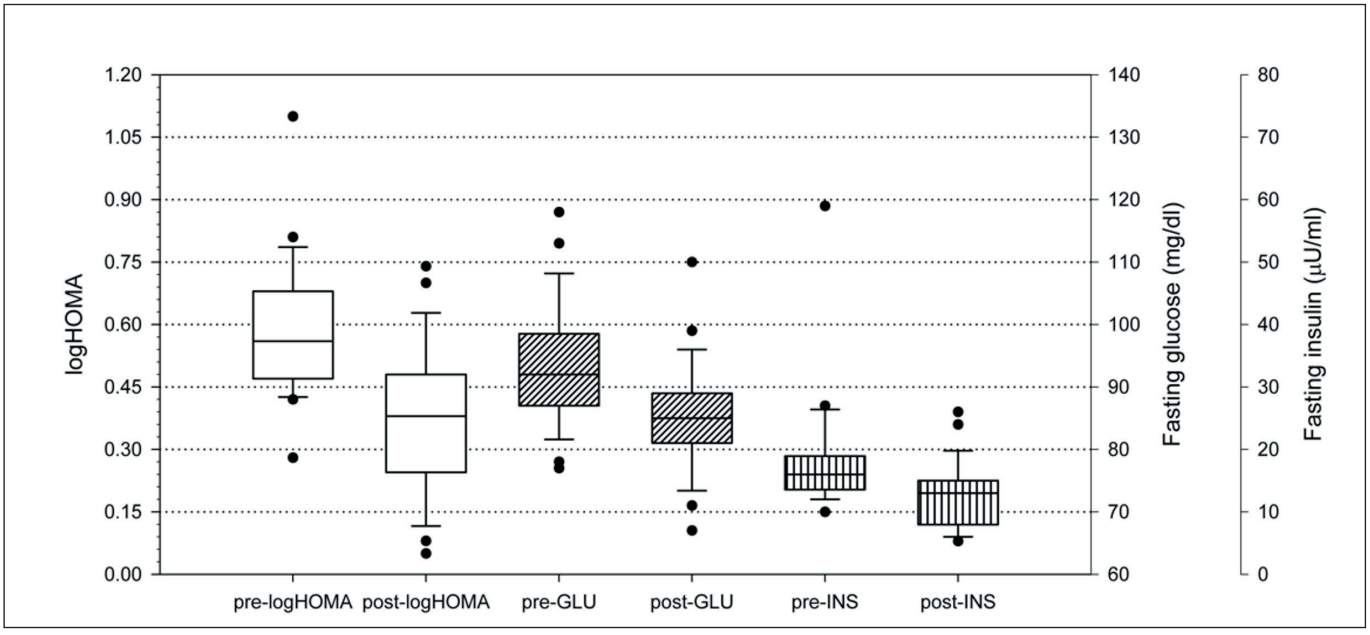


Figure 2: Pretreatment (pre) and posttreatment (post) logHOMA (p<0.001), fasting blood glucose (GLU) (p=0.003), and fasting blood insulin (INS) levels (p=0.02).

cally significant difference was observed between pre- and posttreatment homocysteine levels (p=0.059). Additionally, pre-treatment and posttreatment homocysteine levels among IR and NIR subgroups of patients were within normal range (Table 2).

Insulin resistance

HOMA-IR, logHOMA, QUICKI, ISI_{OGTT}, GI ratio were the calculated insulin sensitivity indices. logHOMA (logarithmic transformation of HOMA-IR) and QUICKI has similar discriminant power comparable to euglycemic hyperinsulinemic clamp (20). Calculation of ISI_{OGTT} is complex but include information about glucose and insulin levels obtained from 75g OGTT. For convenience and ease of calculation logHOMA≥0.5 was used to define insulin resistance. Pre-treatment and posttreatment values of other indices were also compared and calculated for reference purposes (Table 2). All the calculated pre-treatment and posttreatment insulin resistance indices were significantly inter-correlated except ISI_{OGTT} which includes 75g OGTT and repeated insulin measurements.

Number of pre-treatment insulin resistant cases by logHOMA (≥0.5) decreased from 17 patients (68.0%) to 5 patients (20%) after metformin treatment (p=0.004, McNemar test). Pre-treatment fasting blood glucose, insulin and logHOMA values significantly decreased after metformin treatment (Figure 2).

There was no statistically significant correlation between BMI and pre-, posttreatment homocysteine values (pre-treatment: *r*=-0.41, p=0.67; posttreatment: *r*= 0.14, p=0.98). Correspondingly, interrelationship between BMI and pre-, posttreatment logHOMA was not significant (pre-treatment: *r*=-0.11, p=0.61; posttreatment: *r*=-0.21, p=0.31).

DISCUSSION

Polycystic ovary syndrome is known to be associated significant long term health risks including glucose tolerance and type 2 DM, dyslipidaemia (low serum HDL cholesterol, high triglycerides) and cardiovascular disease (6). Considering the frequency of PCOS (6-10%) interventions to prevent these risks should be considered public health

measures. Major factor responsible for long term risks is thought to be insulin resistance and its metabolic consequences. Today insulin sensitizing agents, specifically metformin, were shown to be effective in problems associated with subfertility and menstrual irregularity (8). However, due to lack of proven surrogate markers, evaluation of treatment modalities potentially modifying these risks is difficult. Moreover currently used another group of agents; combined oral contraceptive might have opposite effect due its actions on blood coagulation and blood lipid profile (8). Use of combined oral contraceptive with metformin might also causes difficulty in evaluation of their respective effects on long term. Obesity is also another significant risk factor for cardiovascular and diabetic complications (i.e. insulin resistance) in both normal and PCOS population. However PCOS patients were previously shown to be insulin resistant irrespective of BMI as an estimate of body fat composition (3). Decrease in BMI was shown to have beneficial effects on all aspects of manifestations in PCOS. Therefore, effect of obesity *per se* might be another contributing factor for long term health risks in addition to insulin resistance. In this study we included previously untreated patients to prevent the effect of previous treatments especially combined oral contraceptives. Also, inclusion of lean PCOS patients with BMI <25 kg/m^2 might decrease the independent effect of obesity in parameters.

Hyperhomocysteinemia is extensively accepted as a major independent risk factor for cardiovascular, cerebrovascular, and peripheral vascular disease apart from cholesterol, smoking, and obesity (21). Homocysteine has a direct toxic effect on vascular endothelium by increasing DNA synthesis in vascular smooth muscle cells and inducing its proliferation as well as blocking the regeneration of endothelial cells and causing oxidation of low lipoprotein (22-24).

Women with PCOS were observed to have higher circulating homocysteine levels, implying that disrupted homocysteine metabolism could contribute to the heightened cardiovascular risk reported in this condition (25). Reports regarding homocysteine levels in PCOS are conflicting. Schachter et al. found significantly elevated plasma homocysteine with insulin resistance (14). Furthermore Orio et al. found the normal values of homocysteine levels in PCOS patients (26). In accordance with the results with Orio et al. homocysteine levels were within normal range in this study (Table 1). Study group in Orio et al. was also composed of lean patients with a mean BMI of 24.1±3.1 kg/m^2. Similarly, subgroup analysis Schahter et al. reported minimally increased mean homocysteine levels with a higher BMI of >27 kg/m^2 which according to our opinion inappropriately high cut-off (14). Vrbikova et al. reported increased levels of homocysteine (from 10.1 ± 2.6 to 13.4 ± 5.1) after metformin therapy (27). We couldn't find similar association in our patients (Figure 1, Table 1).

Metformin is a widely used biguanide for the management of type 2 diabetes mellitus. It acts primarily by suppressing hepatic glucose output and improving peripheral insulin sensitivity, and it typically does not induce hypoglycemia when used alone. In women with PCOS, metformin has been reported to enhance insulin sensitivity, reduce circulating insulin and androgen levels, and contribute to a meaningful reduction in BMI (28). However, other investigations have found little or no clinical benefit with metformin therapy (29). A recent review examining metformin for the reproductive and metabolic sequelae of PCOS concluded that current evidence does not clearly justify routine, broad use of metformin in all PCOS patients (30).

Association between IR and elevated homocysteine in specific patient groups in women of reproductive age was investigated by several authors. Elevated levels of homocysteine in both lean and obese PCOS patients were related to IR and not necessarily to body weight (25). But on the other hand, no association between PCO and homocysteine levels was found by Sills et al. According to the study, insulin concentrations were slightly higher in women with polycystic-appearing ovaries, but the difference did not reach statistical significance. Notably, participants were categorized solely by ultrasound ovarian morphology, without considering other diagnostic features of the syndrome (31).

In summary, our study results showed that homocysteine levels in lean PCOS levels were within normal range that treatment with metformin did not affect these levels significantly. Moreover, insulin resistance is a frequent finding which significantly decreased after metformin therapy. Therefore, irrespective of the effects on homocysteine levels metformin is an important agent that decreases insulin resistance that might be beneficial in prevention of long term health risks in lean PCOS patients.

Although metformin significantly improved insulin sensitivity indices (fasting insulin, logHOMA, QUICKI), it did not lead to a measurable change in homocysteine levels. Metformin does not directly interfere with the methionine-homocysteine pathway, and plasma homocysteine is strongly influenced by vitamin B12 and folate status, renal function, genetic polymorphisms, dietary methionine intake and systemic inflammation. In our cohort of lean PCOS patients, baseline homocysteine values were already within the normal range, which may have limited the potential for further pharmacologic reduction despite improved insulin sensitivity.

Metformin has been shown to reduce intestinal absorption of vitamin B12 by approximately 10-30%, and vitamin B12 deficiency may itself lead to elevated homocysteine levels. In the present study, vitamin B12 and folate concentrations were not measured. Therefore, we cannot exclude the possibility that subclinical B12 or folate deficiency may have masked any potential effect of metformin on homocysteine. This represents a major limitation of our study and restricts the strength of conclusions regarding the primary outcome.

The data in this study were collected prospectively between 2004 and 2005. Preparation of the manuscript and submission were delayed due to investigator transitions and archival retrieval processes. Nevertheless, the pathophysiological mechanisms underlying insulin resistance, homocysteine metabolism and cardiovascular risk in PCOS have remained conceptually unchanged, and more recent studies continue to support the role of homocysteine as a vascular risk marker and of metformin as an insulin-sensitizing agent in PCOS (21-25,30). For this reason, we consider that the dataset still provides clinically relevant information, particularly for the lean PCOS phenotype.

The present study has several limitations. First, vitamin B12 and folate levels were not available, which limits our ability to fully interpret homocysteine metabolism under metformin therapy. Second, the relatively small, single-centre sample size restricts the generalizability of our findings. Third, the delay between data collection and publication must be acknowledged as a methodological constraint, although the physiological mechanisms explored remain relevant in contemporary practice.

Acknowledgments

None.

Author's Contributions

All authors contributed equally to the conception, design, data collection, analysis, interpretation, and writing of the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this study.

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Ethics Committee Approval

The study was approved by the Local Ethics Committee of Zonguldak Zonguldak Karaelmas University Hospital (Approval No: 2003/03-3, Date: 03.04.2003). Written informed consent was obtained from all participants prior to enrollment.

Peer-Review Proces

Extremely and externally peer-reviewed.

REFERENCES

1. Parua S, Purkait MP, Bhattacharjee A, Thangarajan R, Rammohan S, Islam K, Bhattacharya K, Syamal AK. Exploring Female Infertility: A Comprehensive Review of Polycystic Ovary Syndrome (PCOS) and Its Impact on Reproductive Health. Obesity Medicine. 2025 May 17:100619.
2. Prosperi S, Chiarelli F. Insulin resistance, metabolic syndrome and polycystic ovaries: an intriguing conundrum. Frontiers in Endocrinology. 2025 Oct 1;16:1669716.
3. Dahan MH, Reaven G. Relationship among obesity, insulin resistance, and hyperinsulinemia in the polycystic ovary syndrome. Endocrine. 2019 Jun;64(3):685-9.
4. Zhu JL, Chen Z, Feng WJ, Long SL, Mo ZC. Sex hormone-binding globulin and polycystic ovary syndrome. Clinica chimica acta. 2019 Dec 1;499:142-8.
5. Qu X, Donnelly R. Sex hormone-binding globulin (SHBG) as an early biomarker and therapeutic target in polycystic ovary syndrome. International journal of molecular sciences. 2020 Nov 1;21(21):8191.
6. Zeng W, Luo Y, Ou J, Gan D, Huang M, Tomlinson B, Jiang Y. Metformin in polycystic ovary syndrome: unraveling multi-stage therapeutic mechanisms from puberty to long-term health outcomes. Frontiers in Pharmacology. 2025 Aug 18;16:1654372.
7. Hincapie MA, Badeghiesh A, Baghlaf H, Dahan MH. Association between pre-gestational diabetes in women with polycystic ovary syndrome and adverse obstetric outcomes. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2025 Jan 1;304:109-14.
8. Nestler JE. Should patients with polycystic ovarian syndrome be treated with metformin?: an enthusiastic endorsement. Hum Reprod 2002;17:1950-1953.
9. Stadtmauer LA, Wong BC, Oehninger S. Should patients with polycystic ovary syndrome be treated with metformin? Benefits of insulin sensitizing drugs in polycystic ovary syndrome--beyond ovulation induction. Hum Reprod 2002;17:3016-3026.
10. van Guldener C, Stehouwer CD. Hyperhomocysteinemia, vascular pathology, and endothelial dysfunction. Semin Thromb Hemost 2000; 26: 281-289.
11. Knekt P, Alfthan G, Aromaa A, et al. Homocysteine and major coronary events: a prospective population study amongst women. J Intern Med 2001; 249: 461-465.
12. Fonseca V, Guba SC, Fink LM. Hyperhomocysteinemia and the endocrine system: implications for atherosclerosis and thrombosis. Endocr Rev 1999;20: 738-759.
13. Schnyder G, Roffi M, Pin R, et al. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. N Engl J Med 2001; 345:1593-1600.
14. Schachter M, Raziel A, Friedler S, Strassburger D, Bern O, Ron-El R. Insulin resistance in patients with polycystic ovary syndrome is associated with elevated plasma homocysteine. Hum Reprod 2003;18: 721-727.

15. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004; 81:19-25.
16. Balen AH, Laven JS, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. Hum Reprod Update 2003; 9: 505-514.
17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-419.
18. Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000; 85: 2402-2410.
19. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999; 22: 1462-1470.
20. Mather KJ, Hunt AE, Steinberg HO, et al. Repeatability characteristics of simple indices of insulin resistance: implications for research applications. J Clin Endocrinol Metab 2001; 86: 5457-5464.
21. Liu M, Fan F, Liu B, Jia J, Jiang Y, Sun P, He D, Liu J, Li Y, Huo Y, Li J. Joint effects of plasma homocysteine concentration and traditional cardiovascular risk factors on the risk of new-onset peripheral arterial disease. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2020;13:3383.
22. Balint B, Jepchumba VK, Guéant JL, Guéant-Rodriguez RM. Mechanisms of homocysteine-induced damage to the endothelial, medial and adventitial layers of the arterial wall. Biochimie. 2020 Jun 1;173:100-6.
23. Steed MM, Tyagi SC. Mechanisms of cardiovascular remodeling in hyperhomocysteinemia. Antioxidants & redox signaling. 2011 Oct 1;15(7):1927-43.
24. Ahmad A, Corban MT, Toya T, Sara JD, Lerman B, Park JY, Lerman LO, Lerman A. Coronary microvascular endothelial dysfunction in patients with angina and nonobstructive coronary artery disease is associated with elevated serum homocysteine levels. Journal of the American Heart Association. 2020 Oct 6;9(19):e017746.
25. Li T, Wu RJ, Liang QQ, Niu LN, Shang Y, Xue LM. Analysis of serum homocysteine concentration in patients less than 35 years of age with polycystic ovary syndrome and hyperandrogenism. Ginekologia Polska. 2022 Aug 23.
26. Orio F Jr, Palomba S, Di Biase S, et al. Homocysteine levels and C677T polymorphism of methylenetetrahydrofolate reductase in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003; 88: 673-679.
27. Vrbikova J, Bicikova M, Tallova J, Hill M, Starka L. Homocysteine and steroids levels in metformin treated women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes 2002; 110: 74-76.
28. Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 1994; 43: 647-654.
29. Acbay O, Gundogdu S. Can metformin reduce insulin resistance in polycystic ovary syndrome? Fertil Steril 1996; 65: 946-949.
30. Sam S, Ehrmann DA. Metformin therapy for the reproductive and metabolic consequences of polycystic ovary syndrome. Diabetologia. 2017 Sep;60(9):1656-61.
31. Sills ES, Genton MG, Perloe M, Schattman GL, Bralley JA, Tucker MJ. Plasma homocysteine, fasting insulin, and androgen patterns among women with polycystic ovaries and infertility. J Obstet Gynaecol Res 2001; 27:163-168.