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Total Antioxidant Capacity and Homocysteine Levels in Obese Women with Polycystic Ovary Syndrome

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Nada Nazar Al-Faris[1]; Fadhil Jawad Al-Tu'ma*[1] and Wasan Ghazi Al-Safi[2]

[1]Department of Biochemistry, College of Medicine, University of Kerbala / Kerbala – Iraq.

[2]Department of Gynecology, College of Medicine, University of Kerbala / Kerbala – Iraq.

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ABSTRACT

Background: Polycystic Ovarian Syndrome (PCOS) is one of the most common metabolic and reproductive disorders among women of reproductive age. Women suffering from PCOS present with a constellation of symptoms associated with menstrual dysfunction and androgen excess, which significantly impacts their quality of life. They may be at increased risk of multiple morbidities, including obesity, insulin resistance, type II diabetes mellitus, cardiovascular disease (CVD), infertility, cancer, and psychological disorders. The relation between polycystic ovary syndrome and cardiovascular disease remains unclear. In an attempt to provide high-quality evidence on the relation between PCOS and CVD, relevant literature for CVD risk marker is homocysteine (Hcy) in women with PCOS was reviewed and analyzed. Polycystic Ovarian Syndrome is associated with oxidative stress, namely increased production of free radicals followed by decreased serum antioxidant levels and antioxidant enzyme activity.**Aim:** This study aimed to evaluate the association between total antioxidant capacity and cardiac biomarker (total homocysteine) in obese polycystic ovary syndrome.**Materials and Methods**: This study carried out from November 2015 till October 2016 a period of case-control study. We included 30 obese patients with signs and symptoms of polycystic ovary syndrome and another 30 obese control subjects. Total cholesterol, triglyceride, HDL-C, LDL-C, VLDL-C, total antioxidant capacity and total homocysteine were determined and calculated in each sample by various techniques. Then various correlations were measured by SPSS system.**Results**: There is a high significant $p < 0.01$ in total antioxidant capacity and total homocysteine when comparison between obese PCOS and obese control. While there is a negative significant correlation between total antioxidant capacity and total homocysteine level in obese PCOS patient.**Conclusions:** Polycystic ovary syndrome patients clearly present a higher risk of cardiovascular diseases spatially obese PCOS patient in addition to that total antioxidant capacity which had a negative correlation with homocysteine levels as cardiac biomarker.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS), refers to hyperandrogenic anovulation (HA), or Stein–Leventhal syndrome (**1**), described since 1935 by Stein and Leventhal (1935), is one of the most common endocrine system disorders that affect women in their reproductive age affecting 7–10% of this group (**2, 3**). The clinical features of the syndrome include oligomenorrhea, acne, hirsutism, obesity and insulin resistance (IR). Insulin resistance is present in the majority of women with PCOS, regardless of Body mass index (BMI), Women with PCOS have an increased risk for impaired glucose tolerance (IGT). IGT or type two diabetes mellitus (T2DM) develops in 40% of obese women with PCOS by the age of 30, decreased high-density lipoprotein cholesterol (HDL-C) levels, and increased total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglyceride levels are also associated with PCOS (**4**). Both polycystic ovary syndrome (PCOS) and cardiovascular disease (CVD) are common in women, CVD remains the leading cause of death in women, and age remains one of the strongest risk factors for the development of atherosclerosis and death from a cardiovascular event **(5)**. Despite the higher prevalence of CV risk factors and subclinical markers of CV disease in women with PCOS, studies have failed to show a consistent association between PCOS and increased CV events or mortality **(6)**. The direct evidence for a link between oxidative stress and cardiovascular disease, ROS-induced oxidative stress plays a role in various cardiovascular diseases such as atherosclerosis, ischemic heart disease, hypertension, cardiomyopathies, cardiac hypertrophy and congestive heart failure **(7)**. Therefore, PCOS is accompanied by oxidative stress in which increased production of free radicals is followed by decreased serum total antioxidant levels. Furthermore, it has been shown that even lean women with PCOS exhibit oxidative stress **(8).** Hyperhomocysteinemia (HHCY) has been described as an independent risk factor for cardiovascular disease. Hyperhomocysteinemia either by elicitation of oxidative stress, systemic inflammation and/or endothelial dysfunction is known to promote insulin resistance and β-cell dysfunction **(9).** Homocysteine (Hcy) in plasma is an independent risk factor for cardiovascular disease. It has often been shown to be related to occlusive vascular disease independently of other known risk factors. Hyperhomocysteinemia induces endothelial injury, oxidative stress, smooth muscle hypertrophy and oxidation of LDL-cholesterol **(10).** Approximately half of all women with PCOS are overweight or obese. Independently of the presence of obesity, these women are frequently insulin resistant and therefore they have hyperinsulinemia, which may play a pathogenic role in the disease **(11).** Recent studies have

documented increased oxidative stress in patients with PCOS **(12, 13),** which may increase the risk of CVD in such patients. Elevated plasma Hcy levels are considered to be an independent risk factor for CVD **(14)**. In recent studies, serum Hcy concentrations were found to be elevated in PCOS women, suggesting that an alteration in Hcy metabolism may play a role in the increased cardiovascular risk associated with PCOS **(15-19).** Hyperhomocysteinaemia-induced oxidative stress may occur as a consequence of either decreased expression and activity of key antioxidant enzymes or increased enzymatic generation of superoxide anions **(20-24).** Mounting data suggest that obesity induces oxidative stress in humans. Several studies have reported increased levels of reactive species or oxidant products in obesity **(25, 26)**. These levels decrease in response to weight reduction, caloric restriction and diets rich in antioxidants **(27, 28)**. Possible contributors to oxidative stress in obesity include hyperglycemia, hyperlipemia, augmented muscle activity to carry excessive weight, hyperleptinemia, chronic inflammation and inadequate antioxidant defenses **(27)**. Oxidative stress is increased in diabetes and also in obesity **(29)**. Studies also demonstrated elevated oxidative stress in insulin-resistant women with PCOS **(12)**. Increased reactive oxygen species generation induced by hyperglycemia and/or hyperinsulinemia has been reported in this population. However, there were conflicting results about the levels of antioxidants in these studies. Some investigators found decreased levels of antioxidants, whereas others have observed increased activities of some antioxidants as a compensatory mechanism in PCOS **(13, 30).**

MATERIALS AND METHODS

The study was conducted during the period from Nov. 2015 to Oct. 2016 a period of case-control study. Sixty women within the reproductive age (18-45 years old). Thirty obese Patient women out of sixty were attended from gynecological and obstetric hospital in Karbala province, and they all diagnosed by their physicians as Polycystic Ovary Syndrome, and they compared with thirty obese healthy control women with comparable age. The study protocol was approved by the ethical research committee of the College of Medicine-University Karbala and Karbala Health Directorate.

Inclusion Criteria

Consisted of all patients with PCOS were already diagnosed and the diagnosis was confirmed according to European society of human reproduction and embryology and American society for reproductive medicine criteria: PCOS is diagnosed if there are any two of the following:

- Presence of polycystic ovary on ultrasound examination.
- Menstrual dysfunction with an ovulation.
- Clinical or biochemical hyperandrogenemia.

Exclusion Criteria

- All patients with hormonal therapy or any medication known to interfere with follicular development or hormonal levels under the study for last 3 months of samples expect metformin.
- All patients with oligomenorrhea, amenorrhea due to other than PCOS causes.
- Diabetic patients.
- All patients suffered from heart diseases or congenital abnormality of the heart.

About 5 ml of venous blood sample was drawn from each patient and control groups. The sera were separated by centrifugation at (3000 runs per minute) for 5 min. Each serum sample was analyzed directly for total cholesterol, Triglyceride, HDL-C, LDL-C, VLDL-C by using Auto Analyzer Biochemistry while then analyzed total antioxidant capacity and total homocysteine by using ELIZA technique.

RESULTS

The results showed a significant difference in total antioxidant capacity, total homocysteine and HDL-C between obese patients and obese healthy $P < 0.01$ as shown in Table 1. There was statistically negative significant correlation between T-AOC and HCY as shown in Table 2 and figure 1.

Table 1: Comparison between obese polycystic ovary syndrome patient group and obese control group in the measured parameter

Parameter	Control group N= 60 Mean ± SE	Patient group N= 60 Mean ± SE	P value
Age (20 – 35)	27.733 ± 3.808	26.3833 ± 4.741	NS
BMI (Kg/m²)	28.217 ± 5.197	28.891 ± 5.957	NS
Cholesterol (mg/dl)	139 ± 21.637	141.082 ± 23.322	NS
TG (mg/dl)	83.753 ± 32.172	85.458 ± 39.089	NS
HDL-C (mg/dl)	54.51 ± 5.72	41.747 ± 9.387	P< 0.01
LDL-C (mg/dl)	73.101 ± 10.38	78.295 ± 12.95	P< 0.05
VLDL-C (mg/dl)	16.75 ± 6.434	17.091 ± 7.817	NS
T-AOC (U/ml)	26.029 ± 20.515	10.783 ± 5.039	P< 0.01
HCY (nmol/ml)	14.411 ± 13.732	7.392 ± 2.407	P< 0.01

Table (2): Correlation between T-AOC and HCY

T-AOC (U/ml)	HCY (nmol/ml)
	r = - 0.342 p = 0.045

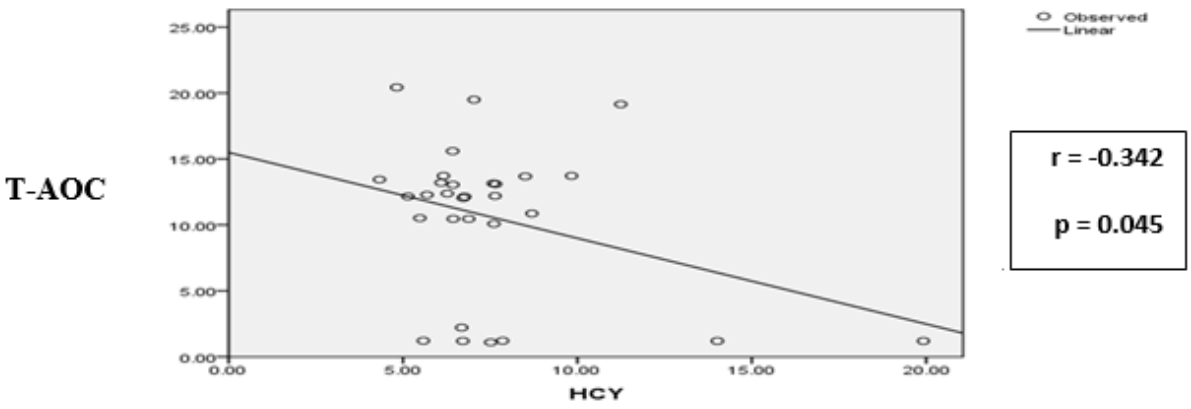

Figure 1: Correlation between T-AOC and HCY in obese PCOS.

DISCUSSION

The results indicated that homocysteine levels were significantly elevated in obese PCOS patients. These findings were agreeing with many studies (**31–33**). Homocysteine may have several actions on vascular cells impairment of endothelial function, enhancement of low-density lipoprotein oxidation, promotion of smooth muscle cell proliferation and accelerated elastin degradation, as a result of increased free radical generation leading to a reduction in total antioxidant capacity in woman with PCOS. It was also observed that elevated serum Hcy levels are present in PCOS women, suggesting that an alteration in Hcy metabolism may be implicated in the increased risk of cardiovascular disease in such patients (**16**). Lowering plasma Hcy improves endothelial function in individuals with coronary artery disease and decreases the incidence of major cardiac events (**34**). This is lead to widely accept that Hcy is a major independent risk factor for cardiovascular disease (**35**). Also, the results showed high significant differences in total antioxidant capacity between patient and control. Fenkci *et al.* detected lower TAOC levels in the PCOS group, but these levels did not reach a level of statistical significance. This observation suggested that the oxidative status imbalance in PCOS women might contribute to their increased risk of cardiovascular diseases. Polycystic ovary syndrome is also associated with decreased antioxidant concentrations and is thus considered an oxidative state (**36**). Therefore the result indicated that the correlation between TAOC and HCY is a significant negative correlation in obese PCOS. This is due to the influential factors is obesity, where they considered as a positive impact on oxidative stress (**37, 38**).

CONCLUSION

Polycystic ovary syndrome patients clearly present a higher risk of cardiovascular diseases. Obesity appeared to be a major factor associated with elevated cardiac markers. Homocysteine was high in PCOS patient. From the presented results which revealed that PCOS is associated with dyslipidemia and altered oxidative status. Total antioxidant capacity had a negative correlation with Homocysteine in obese women.

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REFERENCES

1. El Hayek, S., Bitar, L., Hamdar, L. H., Mirza, F. G., & Daoud, G. (2016). Polycystic Ovarian Syndrome: An Updated Overview. *Frontiers in physiology*, *7*.
2. Azziz, R., Woods, K. S., Reyna, R., Key, T. J., Knochenhauer, E. S., & Yildiz, B. O. (2004). The prevalence and features of the polycystic ovary syndrome in an unselected population. *The Journal of Clinical Endocrinology & Metabolism*, *89*(6), 2745-2749.
3. Saxena, R., Georgopoulos, N. A., Braaten, T. J., Bjonnes, A. C., Koika, V., Panidis, D., & Welt, C. K. (2015). Han Chinese polycystic ovary syndrome risk variants in women of European ancestry: relationship to FSH levels and glucose tolerance. *Human Reproduction*, dev085.
4. Halperin, I. J., Kumar, S. S., Stroup, D. F., & Laredo, S. E. (2010). The association between the combined oral contraceptive pill and insulin resistance, dysglycemia and dyslipidemia in women with polycystic ovary syndrome: a systematic review and meta-analysis of observational studies. *Human Reproduction*, deq301.
5. Legro, R. S. (2003). Polycystic ovary syndrome and cardiovascular disease: a premature association?. *Endocrine reviews*, *24*(3), 302-312.

6. Legro, R. S., Arslanian, S. A., Ehrmann, D. A., Hoeger, K. M., Murad, M. H., Pasquali, R., & Welt, C. K. (2013). Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, *98*(12), 4565-4592.
7. Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *The international journal of biochemistry & cell biology*, *39*(1), 44-84.
8. Savic-Radojevic, A., Antic, I. B., Coric, V., Bjekic-Macut, J., Radic, T., Zarkovic, M., & Simic, T. (2015). Effect of hyperglycemia and hyperinsulinemia on glutathione peroxidase activity in non-obese women with polycystic ovary syndrome. *Hormones*, *14*(1), 101-108.
9. Chauhan, G., Kaur, I., Tabassum, R., Dwivedi, O. P., Ghosh, S., Tandon, N., & Bharadwaj, D. (2011). Common variants of homocysteine metabolism pathway genes and risk of type 2 diabetes and related traits in Indians. *Experimental diabetes research*, *2012*.
10. Bamashmoos, S. A., Al-Nuzaily, M. A., Al-Meeri, A. M., & Ali, F. H. (2013). Relationship between total homocysteine, total cholesterol and creatinine levels in overt hypothyroid patients. *Springerplus*, *2*(1), 1.
11. Yilmaz, M., Bukan, N., Ayvaz, G., Karakoç, A., Törüner, F., Çakir, N., & Arslan, M. (2005). The effects of rosiglitazone and metformin on oxidative stress and homocysteine levels in lean patients with polycystic ovary syndrome. *Human Reproduction*, *20*(12), 3333-3340.
12. Sabuncu, T., Vural, H., Harma, M., & Harma, M. (2001). Oxidative stress in polycystic ovary syndrome and its contribution to the risk of cardiovascular disease. *Clinical biochemistry*, *34*(5), 407-413.
13. Fenkci, V., Fenkci, S., Yilmazer, M., & Serteser, M. (2003). Decreased total antioxidant status and increased oxidative stress in women with polycystic ovary syndrome may contribute to the risk of cardiovascular disease. *Fertility and sterility*, *80*(1), 123-127.
14. Clarke R, Daly L, Robinson K, Naughten E, Cahalane S, Fowler B and Graham I (1991) Hyperhomocysteinemia: an independent risk factor for vascular disease. N Engl J Med 324,1149–1155
15. Loverro, G., Lorusso, F., Mei, L., Depalo, R., Cormio, G., & Selvaggi, L. (2002). The plasma homocysteine levels are increased in polycystic ovary syndrome. *Gynecologic and obstetric investigation*, *53*(3), 157-162.
16. Randeva, H. S., Lewandowski, K. C., Drzewoski, J., Brooke-Wavell, K., O'Callaghan, C., Czupryniak, L., & Prelevic, G. M. (2002). Exercise decreases plasma total homocysteine in overweight young women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism*, *87*(10), 4496-4501.
17. Vrbikova J, Bicikova M. Tallova J, Hill M and Starka L (2002) Homocysteine and steroid levels in metformin-treated women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes 110,74–77.
18. Schachter M, Raziel A, Friedler S, Strassburger D, Bern O and Ron-El R (2003) Insulin resistance in patients with polycystic ovary syndrome is associated with elevated plasma homocysteine. Hum Reprod 18,721–727.
19. Wijeyaratne CN, Nirantharakumar K, Balen AH, Barth JH, Sheriff R and Belchetz PE (2004) Plasma homocysteine in polycystic ovary syndrome: does it correlate with insulin resistance and ethnicity? Clin Endocrinol (Oxf) 60,560–567.
20. Eberhardt RT, Forgione MA, Cap A, Leopold JA, Rudd MA, Trolliet M, Heydrick S, Stark R, Klings ES, Moldovan NI (2000) Endothelial dysfunction in a murine model of mild hyperhomocyst(e)inemia. J Clin Invest 106,483–491.
21. Lentz SR, Erger RA, Dayal S, Maeda N, Malinow MR, Heistad DD and Faraci FM (2000) Folate dependence of hyperhomocysteinemia and endothelial dysfunction in cystathionine synthase-deficient mice. Am J Physiol 279, H970–H975.
22. Faraci FM (2003) Hyperhomocysteinemia: a million ways to lose control. Arterioscler Thromb Vasc Biol 23,371–373.
23. Loscalzo J (2003) Oxidant stress: a key determinant of atherothrombosis. Biochem Soc Trans 31,1059–1061.
24. Ungvari Z, Csiszar A, Edwards JG, Kaminski PM, Wolin MS, Kaley G and Koller A (2003) Increased superoxide production in coronary arteries in hyperhomocysteinemia: role of TNF-□ , NAD(P)H oxidase and iNOS. Arterioscler Thromb Vasc Biol 23,418–424.
25. Konukoglu D, Serin O, Ercan M, Turhan MS. Plasma homocysteine levels in obese and non-obese subjects with or without hypertension; its relationship with oxidative stress and copper. Clin Biochem 2003;36:405–408.
26. Urakawa H, Katsuki A, Sumida Y, Gabazza EC, Murashima S, Morioka K. Oxidative stress is associated with adiposity and insulin resistance in men. J Clin Endocrinol Metab 2003;88:4673–4676.

27. Vincent HK, Taylor AG. Biomarkers and potential mechanisms of obesity-induced oxidant stress in humans. Int J Obes 2005;30:400–418.
28. Murri, M., García-Fuentes, E., García-Almeida, J. M., Garrido Sánchez, L., Mayas, M. D., Bernal, R., *et al*., (2010). Changes in oxidative stress and insulin resistance in morbidly obese patients after bariatric surgery. *Obesity surgery*, *20*(3): 363-368.
29. Uchida Y, Ohba K, Yoshioka T, Irie K, Muraki T, Maru Y (2004). Cellular carbonyl stress enhances the expression of plasminogen activator inhibitor-1 in rat white adipocytes via reactive oxygen species dependent pathway. J Biol Chem, 279: 4075–4083.
30. Dincer Y, Akcay T, Erdem T, Saygili EI, Gundogdu S (2005). DNA damage, DNA susceptibility to oxidation and glutathione level in women with polycystic ovary syndrome. Scand J Clin Lab Invest, 65: 721–728.
31. Karaer, A.; Cavkaytar, S.; Mert, I.; Buyukkagnici, U., and Batioglu, S. (2010). Cardiovascular risk factors in polycystic ovary syndrome. *Journal of Obstetrics and Gynaecology*, *30*(4): 387-392.
32. Mohamadin, A.; Habib, F. and Al-Saggaf A. (2010). Cardiovascular disease markers in women with polycystic ovary syndrome with emphasis on asymmetric dimethylarginine and homocysteine. *Annals of Saudi medicine*, *30*(4): 278.
33. Pamuk, B. O.; Torun, A. N.; Kulaksizoglu, M.; Ertugrul, D.; Ciftci, O., Kulaksizoglu, S. *et al*., (2010). Asymmetric dimethylarginine levels and carotid intima-media thickness in obese patients with polycystic ovary syndrome and their relationship to metabolic parameters. *Fertility and sterility*, *93*(4): 1227-1233.
34. Schnyder, G.; Roffi, M.; Pin, R.; Flammer, Y.; Lange, H.; Eberli, F. R. *et al*., (2001). Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. *New England Journal of Medicine*, *345*(22): 1593-1600.
35. Hankey GJ. and Eikelboom JW.(1999). Homocysteine and vascular disease. Lancet 354:407–413.
36. Palacio, J. R.; Iborra, A.; Ulcova-Gallova, Z.; Badia, R., and Martinez, P. (2006). The presence of antibodies to oxidative modified proteins in serum from polycystic ovary syndrome patients. *Clinical & Experimental Immunology*,*144*(2): 217-222.
37. Verit, F. F. and Erel, O. (2008). Oxidative stress in nonobese women with polycystic ovary syndrome: correlations with endocrine and screening parameters. *Gynecologic and obstetric investigation*, *65*(4): 233-239.
38. Menon, V.; Ram, M.; Dorn, J.; Armstrong, D.; Muti, P.; Freudenheim, J. L. *et al*., (2004). Oxidative stress and glucose levels in a population-based sample. *Diabetic medicine*, *21*(12), 1346-1352.