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Association between oxidative stress, antioxidant enzymes, and homocysteine in patients with polycystic ovary syndrome

A.H. ALFEEL[1], S.E.O. HUSSEIN[1], T.Y. ELSAYED YOUSIF[2], A.M.A. BABKER[1], A.E. ALAMIN ALTOUM[1], A.N. MOHAMED[3], H.O. ELZEIN[4], T. AHMED[5], M. SABOOR[6], H.A. OSMAN[7], P. KUMAR[8], H. ALI[9], E.K. ABDALHABIB[10]

[1]Department of Medical Laboratory Sciences, College of Health Sciences, Gulf Medical University, Ajman, United Arab Emirates
[2]Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, Jazan University, Jazan, Saudi Arabia
[3]Department of Clinical Chemistry, Alfalah Medical Polyclinic, Taif, Saudi Arabia
[4]Department of Medical Laboratory Technology, College of Applied Medical Sciences, Northern Border University, Arar, Saudi Arabia
[5]Anatomy Department, Faculty of Medicine, Jazan University, Jazan, Saudi Arabia
[6]Department of Medical Laboratory Sciences, College of Health Sciences, University of Sharjah, Sharjah, UAE
[7]Faculty of Medical and Health Sciences, Liwa College, Abu Dhabi, UAE
[8]College of Health Sciences, Gulf Medical University, Ajman, United Arab Emirates
[9]Medical Laboratory Sciences College, University of Gezira, Wad Medani, Sudan
[10]Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, AlQurayyat -Jouf University, Jouf, Saudi Arabia

Abstract. – OBJECTIVE: Polycystic ovary syndrome (PCOS) is a prevalent health condition that commonly affects adolescent girls and young women. The purpose of this study was to evaluate the correlation between levels of total glutathione (TG), reduced glutathione (GSH), superoxide dismutase (SOD), lipid peroxidation, and homocysteine with PCOS.

PATIENTS AND METHODS: This study employed a cross-sectional case-control design, involving a target population of 305 Sudanese females. Among them, 205 individuals were categorized as cases, and 100 served as controls. The TG, GSH, SOD, lipid peroxidation, and homocysteine levels were measured in the serum of study participants through enzyme-linked immunosorbent essay.

RESULTS: Total glutathione (1,174.5 ± 271.4 *vs.* 986.1 ± 191.5, $p = 0.01$), GSH (801.3 ± 132.2 *vs.* 748.6 ± 103.1, $p = 0.007$), SOD (225.2 ± 57.8 *vs.* 195.5 ± 49.6, $p = 0.009$), lipid peroxidation (3.4 ± 1.1 *vs.* 2.4 ± 0.7, $p = 0.03$), and homocysteine (14.9 ± 2.1 *vs.* 13.5 ± 1.6, $p = 0.04$), showed significant differences between the two groups (cases *vs.* controls). A moderate positive correlation between TG, GSH, SOD, lipid peroxidation, homocysteine, BMI, age, and duration of PCOS was observed. Furthermore, a strong positive correlation between BMI, age, and duration of PCOS was noted within the patient group.

CONCLUSIONS: In conclusion, this study demonstrates that patients with PCOS have elevated levels of TG, GSH, SOD, lipid peroxidation, and homocysteine compared to the control group. These findings suggest a potential association between PCOS and oxidative stress, lipid metabolism, and homocysteine pathways. Moreover, the observed positive correlation with BMI, age, and duration of PCOS indicates the importance of these factors in disease progression.

Key Words:
Oxidative stress, Antioxidant enzyme, Polycystic ovary syndrome, Homocysteine.

Introduction

Infertility is common among young females and women of childbearing age[1]. One of the significant causes of infertility is polycystic ovary syndrome (PCOS)[1], also known as Stein-Leventhal syndrome. PCOS is a heterogeneous and commonly occurring endocrinopathy, with a prevalence ranging from 5-21% among reproductive-aged women[2,3]. It is associated with a wide spectrum of complications affecting various aspects of health,

Corresponding Author: Muhammad Saboor, Ph.D; e-mail: M.Ahmed@sharjah.ac.ae

including reproductive, metabolic, and psychological features. Although the exact etiology of PCOS is unknown, its pathogenesis involves several mechanisms that have been suggested to contribute to its development. These include hormonal imbalance, hyperandrogenism, resistance to insulin, genetic inheritance[4], polycystic ovaries, oligoanovulation[3,5], and environmental factors (obesity, infections, and toxins)[6].

PCOS is characterized by hyperandrogenism that can manifest during prenatal development and contribute to the development of android-type abdominal obesity[7]. Excessive weight and obesity have deleterious consequences on the process of ovulation and can lead to the onset or worsening of insulin resistance (IR) and hyperandrogenism. The progressive disorders that arise in the context of obesity are marked by augmented adipogenesis and impaired lipolysis. The intricate interplay between adipose tissues and ovarian function gives rise to disturbances in folliculogenesis. Furthermore, obesity triggers the secretion of proinflammatory adipokines, which exert their influence on thecal cells and disrupt the production of androgens[8]. Excessive androgen production in the ovarian thecal cells is hypothesized to stem from persistent acyclic stimulation by luteinizing hormone (LH), while a relative deficiency of follicle-stimulating hormone (FSH) is implicated in chronic anovulation[9]. Ovarian hyperandrogenism leads to impairments in follicle selection, maturation, and ovulation processes. The absence of ovulation leads to menstrual irregularities and infertility, stemming from insufficient gestagen levels and relative hyperestrogenism. These hormonal imbalances elevate the susceptibility to estrogen-dependent cancers[10].

Oxidative stress (OS) is characterized by an imbalance between oxidants and antioxidants in the body that results in the generation of excessive amounts of reactive oxygen species (ROS)[11]. At lower concentrations, ROS and nitrogen species play a crucial role in effectively combating infectious agents. However, their increased levels can lead to detrimental effects, causing damage to DNA, cellular lipids, and proteins[12]. Hence, the body employs various mechanisms to counteract the effects of ROS, including antioxidants e.g., superoxide dismutase, glutathione peroxides, catalase, vitamin E, and ascorbic acid[13].

Oxidative stress is increasingly recognized as a central player in the pathophysiology of various disorders. It has been suggested that oxidative stress might play a role in the pathogenesis of PCOS, as substantiated by significantly elevated levels of oxidative markers in circulation[14]. Metabolic disruptions in PCOS lead to an upsurge of free radicals. In PCOS, OS is influenced by several factors, such as hyperandrogenemia, IR, genetic and/or environmental factors, and obesity, particularly abdominal obesity. Assessing OS and antioxidant biomarkers has been proposed as a valuable means to estimate the risk of oxidative damage and related diseases. Such evaluations can provide valuable insights for the prevention and management of oxidative disorders[15]. There is compelling evidence to suggest that decreased antioxidant capacity may contribute to the increased risk of cardiovascular diseases (CVD) in women with PCOS[16]. In addition to well-established risk factors such as IR, age, hypertension, obesity, and dyslipidemia, the compromised antioxidant status observed in PCOS appears to play a role in the development of CVD[17].

Malondialdehyde (MDA) is a stable biomarker derived from the lipid peroxidation of polyunsaturated fatty acids. It is commonly employed as a reliable indicator of oxidative damage. It is generated as a consequence of lipid peroxidation, resulting in increased levels in response to elevated production of ROS. Consequently, MDA serves as a valuable tool for assessing the effectiveness of antioxidant therapy in mitigating oxidative damage[18].

Homocysteine is an α-amino acid that is not commonly found in dietary sources. It is considered nonproteinogenic in the human body, being synthesized through a series of intricate biochemical reactions[19]. Homocysteine is widely recognized as a reliable marker of OS due to its capability to stimulate the generation of ROS. Elevated levels of homocysteine can lead to endothelial cell damage and dysfunction, contributing to the development of various cardiovascular conditions[14,20]. Indeed, elevated homocysteine level has emerged as an important risk factor in assessing CVD[21].

Although the OS and antioxidant activity in patients with PCOS has been widely addressed in the literature, conflicting data prevails. Additionally, there is a gap in associating these markers with BMI, age, and duration of PCOS. Hence, the present study aimed to evaluate the correlation between the levels of oxidative stress markers [antioxidant enzymes [glutathione (GSH), superoxide dismutase (SOD)], lipid peroxidation (malondialdehyde - MDA), and homocysteine in patients with PCOS and association of these markers with BMI, age, and duration of PCOS.

Patients and Methods

This was a descriptive cross-sectional analytical case-control study conducted in Khartoum state, Sudan. The ethical approval of the study was granted by the Ethical Review Board, University of Science and Technology (U.S.T), College of Graduate Studies and Academic Advancement, Omdurman, Sudan (Reference No. J.A.T/K.A.M.T/M.A/2016). The study was conducted in accordance with the guidelines of the Declaration of Helsinki. Informed consent was obtained from the study participants. The target population consisted of 305 Sudanese females. The study participants were grouped into cases (205) and controls (100). Cases were females diagnosed with PCOS. The total sample size was calculated using G*Power software to be 176, with an additional 10% added for potential dropouts, resulting in a target of 193 samples. However, we collected 205 samples. For the diagnosis of PCOS, Rotterdam criteria[22] / ESHRE/ASRM criteria[23] were followed i.e., the presence of at least two out of three key features: irregular menstrual cycles or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries observed on ultrasound. Patients with PCOS having hypertension, diabetes, cancer, ischemic heart diseases, renal diseases, autoimmune diseases, and thyroid diseases were excluded from the study. Subjects with a history of receiving anti-inflammatory drugs in the last 6 months and a history or symptoms of any other stress-induced disorder were also excluded from the study. Additionally, females with hyperprolactinemia were also excluded from the study. The control group contained females of the same age range without any clinical condition.

The participants were classified according to the World Health Organization (WHO) body mass index (BMI) classification[24] and were aged between 21 and 45 years. Venous blood samples (7 ml) were collected from fasting subjects of both groups after they gave informed consent and completed the questionnaire. The samples were collected in lithium heparin tubes and plain tubes. The blood collected in a heparinized tube was gently mixed with the anticoagulant. The collected blood was used immediately for testing glutathione. After glutathione estimation, the whole blood was centrifuged, and plasma was separated and preserved at -20°C prior to further processing. The preserved plasma was used for testing SOD. The serum was obtained by centrifuging the samples collected in the plain tubes at 10,000 rpm for 10 minutes at -4°C using a cold centrifuge. Serum samples were used for testing homocysteine and lipid peroxidation (malondialdehyde). Body mass index was determined through anthropometric measurements, including height and weight, following standard WHO protocols. BMI was calculated as weight (in kilograms) divided by height (in meters squared). Homocysteine, glutathione, SOD, and lipid peroxidation were estimated by ELISA Kits-(ab228559), (ab22604), (ab119520), and (ab233471) SimpleStep ELISA® kits (Abcam, MA, USA).

Statistical Analysis

The results were analyzed using Statistical Package for the Social Sciences Version 24 (IBM Corp., Armonk, NY, USA). The mean and standard deviation (SD) were calculated, and independent *t*-tests were employed for comparisons. Linear regression was also performed to assess correlations. Tests of normality, including the Kolmogorov-Smirnov and Shapiro-Wilk tests, were employed to assess whether the data follows a normal distribution for statistical analysis. The *p*-value was obtained to determine the significance of the results, with a p-value < 0.05 considered statistically significant.

Results

This study involved 205 females with PCOS and 100 normal healthy females. The age range of females in both groups was between 21 and 45 years. The duration of PCOS ranged from 5 to 13 years. Patients with PCOS were grouped based on BMI according to the WHO BMI Classification (Tables I and II). Total glutathione levels were measured as 1,174.5 ± 271.4 in the PCOS group and 986.1 ± 191.5 in the non-PCOS group, with a statistically significant difference ($p = 0.01$). Similarly, GSH levels were measured as 801.3 ± 132.2. in the PCOS group and 748.6 ± 103.1 in the non-PCOS group ($p = 0.007$). Superoxide dismutase levels were 225.2 ± 57.8 in the PCOS group and 195.5 ± 49.6 in the non-PCOS group, with a significant difference ($p = 0.009$). Lastly, lipid peroxidation levels were 3.4 ± 1.1 in the PCOS group and 2.4 ± 0.7 in the non-PCOS group ($p = 0.03$) (Table III). Homocysteine levels were 14.9 ± 2.1 in the PCOS group vs. 13.5 ± 1.6 in the non-PCOS group ($p = 0.04$). Based on the findings, there was a moderate positive correla-

Table I. Distribution of patients with polycystic ovary syndrome based on *BMI.

Categories Based on BMI	Body Mass Index (Kg/m²)	Number of patients with polycystic ovary syndrome	% of patients with polycystic ovary syndrome
Underweight	< 8.5	17	8%
Healthy weight	18.5 - 24.9	61	29%
Overweight	25 - 29.9	98	49%
Obesity	30 - 39.9	26	12%
Severe obesity	> 40	3	2%

*BMI=Body Mass Index.

Table II. Sociodemographic data of females with polycystic ovary syndrome based on BMI.

	Age/Year		Body Mass Index-Kg/m²		Duration of disease/years	
Variable	Range	mean ± SD*	Range	mean ± SD*	Range	mean ± SD*
Underweight	25 - 45	41.7 ± 5.8	17.1 - 18.3	16.8 ± 1.9	8 - 10	9.8 ± 1.7
Healthy weight	23 - 42	39.6 ± 4.2	19 - 24.9	19.3 ± 1.7	5 - 9	8.6 ± 1.5
Overweight	28 - 44	38 ± 3.6	25.2 - 28.8	27.1 ± 2.2	9 - 12	11.1 ± 2.4
Obesity	21 - 45	40.1 ± 5.4	30.1 - 33.7	31.4 ± 3.7	7 - 11	10.0 ± 1.9
Severe obesity	22 - 43	37.4 ± 3.1	40.7 - 40.9	41.1 ± 4.0	9 - 13	11.8 ± 2.8

*SD: Standard deviation; BMI=Body Mass Index.

Table III. Comparison of the biochemical parameter's means among the study groups.

	Compared means between patients and control groups			
Variable	Range	(mean ± SD) (Polycystic Ovary)	(mean ± SD) (Non-Polycystic Ovary)	*p
Total Glutathione	723.5 - 1,293.7	1,174.5 ± 271.4	986.1 ± 191.5	0.01
Reduced Glutathione	486.1 - 962.4	801.3 ± 132.2	748.6 ± 103.1	0.007
Superoxide dismutase	206.1 - 309.4	225.2 ± 57.8	195.5 ± 49.6	0.009
Lipid peroxidation	1.3 - 6.2	3.4 ± 1.1	2.4 ± 0.7	0.03
Homocysteine	10.1 - 20.8	14.9 ± 2.1	13.5 ± 1.6	0.04

Independent *t*-test was employed for statistical analysis. * $p < 0.05$ (significant).

tion between TG, GSH, SOD, lipid peroxidase, homocysteine, BMI, age, and duration of PCOS (Table IV). Additionally, there was a strong positive correlation found specifically between BMI, age, and duration of PCOS (Figures 1, 2, 3, 4, 5).

Discussion

One of the most prevalent endocrine disorders in women of reproductive age is PCOS. GSH, a crucial antioxidant, undergoes cytosolic synthesis involving two adenosine triphosphate (ATP)-dependent steps. The first step involves the conversion of glutamate and cysteine by γ-glutamylcysteine synthetase to γ-glutamylcysteine. The second step entails the combination of γ-glutamylcysteine and glycine by GSH synthetase, resulting in the formation of GSH. GSH is distributed across various cellular compartments, such as the endoplasmic reticulum, nucleus, and mitochondria[25]. Its vital functions include the regulation of disulfide bonds of proteins and the elimination of electrophiles and oxidants[26]. The redox-active thiol group of GSH plays a central role in its antioxidant activity, as it becomes oxidized while reducing target molecules. GSH serves as a direct scavenger of ROS and is also involved as a substrate for GSH peroxidase, which reduces hydrogen peroxide[27].

With a total of 305 participants, 205 being cases and 100 controls, this study revealed a significant

Table IV. Biomarkers correlation in females with polycystic ovary syndrome.

	Age		Body Mass Index		Duration of disease	
Variable	***R**	****p**	***R**	****p**	***R**	****p**
Total Glutathione	0.48	0.03	0.54	0.01	0.49	0.009
Reduced Glutathione	0.53	0.013	0.49	0.023	0.71	0.03
Superoxide dismutase	0.59	0.046	0.70	0.043	0.64	0.026
Lipid peroxidation	0.61	0.026	0.51	0.007	0.55	0.02
Homocysteine	0.60	0.007	0.61	0.041	0.52	0.048

*R = Correlation coefficient. ** $p < 0.05$ (significant).

increase in total glutathione and GSH activity among patients with PCOS compared to the control group. This increased GSH activity is believed to be a response to counteract the effects of increased OS observed in PCOS. The literature on GSH levels in patients with PCOS has shown varied results in comparison to the present study. Previous studies[28] have indicated that patients with PCOS have lower GSH levels compared to healthy individuals, and this decrease in GSH has been associated with IR and mitochondrial dysfunction. Similarly, in a study involving young nonobese women, lower GSH levels were observed regardless of IR status[29]. Another study[30] reported significantly reduced activity of GSH peroxidase (GPx) in PCOS women compared to controls, highlighting the need for further investigations to elucidate the role of GPx as an antioxidant defense in PCOS.

In another study[31], both GSH and GPx levels were significantly lower in the PCOS group compared to the control group, particularly in obese patients with PCOS. Furthermore, a negative correlation was found between the waist-hip ratio and these two antioxidant levels. These findings suggest that low GSH levels contribute to OS in PCOS patients. Consistent with the literature, Dinger et al[32] reported a significant decrease in

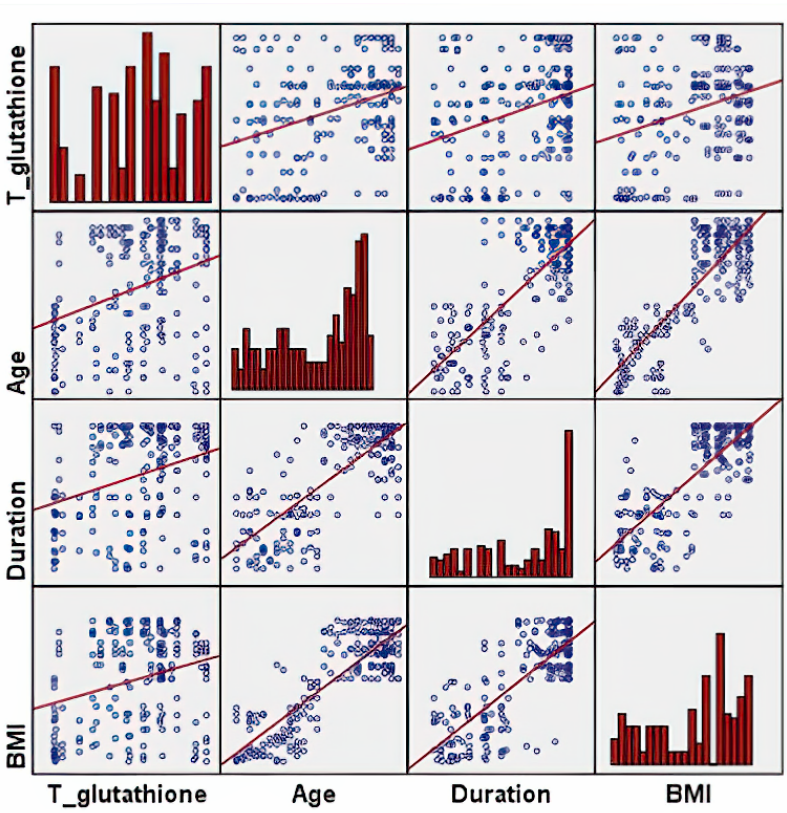

Figure 1. Moderate positive correlation between Total Glutathione, BMI, age, and duration of PCOS compared with a strong positive correlation between BMI, age, and duration of PCOS.

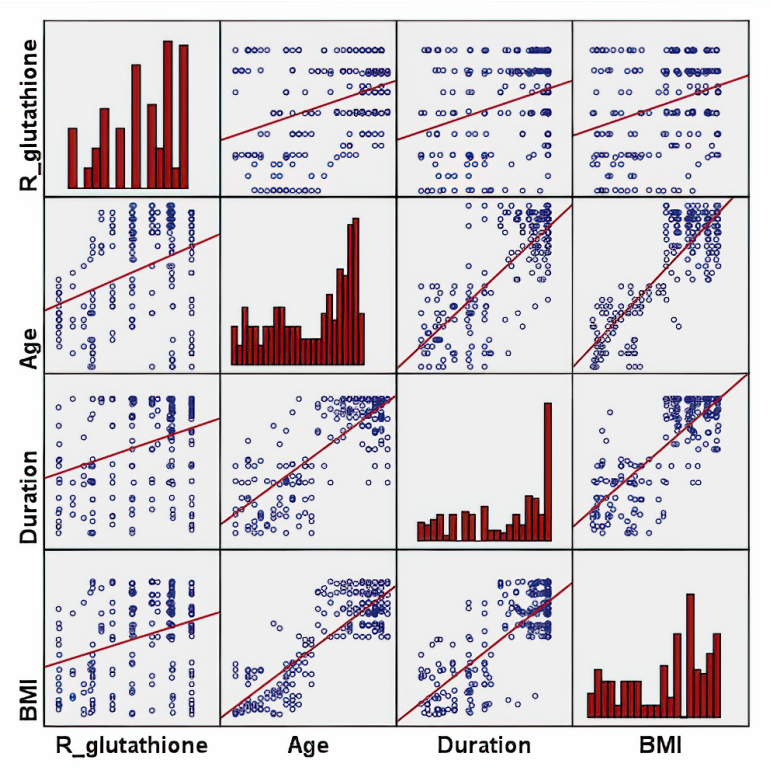

Figure 2. Moderate positive correlation between Reduced glutathione, BMI, age, and duration of PCOS compared with a strong positive correlation between BMI, age, and duration of PCOS.

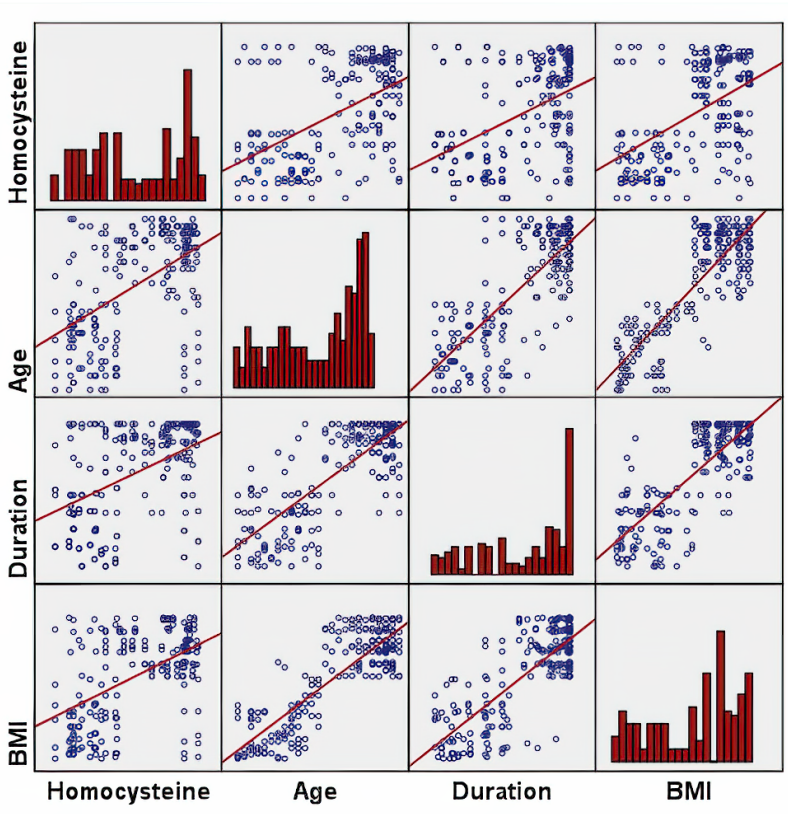

Figure 3. Moderate positive correlation between Homocysteine, BMI, age, and duration of PCOS compared with a strong positive correlation between BMI, age, and duration of PCOS.

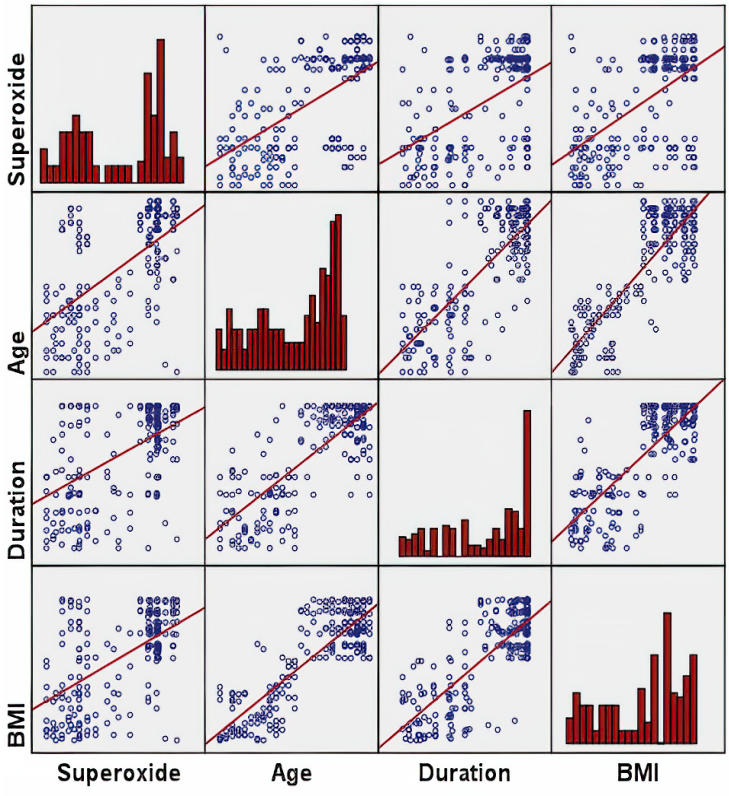

Figure 4. Moderate positive correlation between Superoxide dismutase, BMI, age, and duration of PCOS compared with a strong positive correlation between BMI, age, and duration of PCOS.

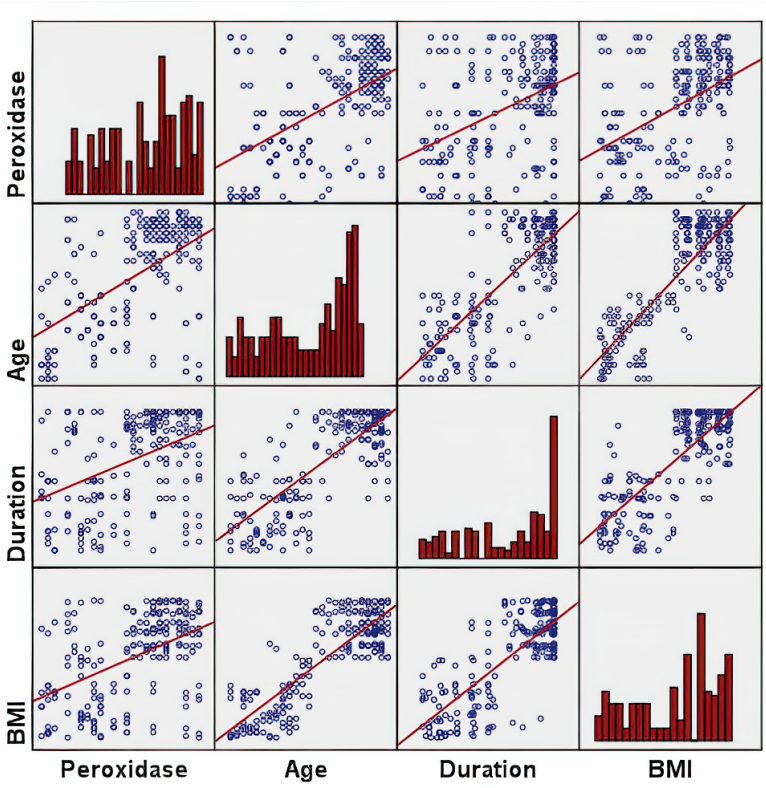

Figure 5. Moderate positive correlation between Lipid peroxidase, BMI, age, and duration of PCOS compared with a strong positive correlation between BMI, age, and duration of PCOS.

GSH levels in women with PCOS compared to the control group. They hypothesized that the reduction in GSH may be attributed to heightened ROS production in PCOS patients.

In the current study, patients with PCOS exhibited significantly better antioxidant (SOD) activity as compared to controls. SOD is an important antioxidant enzyme that plays a crucial role in neutralizing harmful anions. The increased activity of SOD observed in patients with PCOS may represent an adaptive response to counteract the effects of OS. It facilitates the dismutation of superoxide anions into less harmful hydrogen peroxide. Furthermore, significantly high levels of SOD have been noted in the PCOS group compared to the control group[14,33,34]. This finding suggests that PCOS may lead to an upregulation of SOD activity as a compensatory mechanism and a potential adaptive response to counteract the increased generation of ROS associated with the condition.

Contrary to these findings, a study by Nawrocka-Rutkowska et al[35] found no significant difference in SOD levels between the studied groups, likely due to the presence of IR and obesity. It was suggested that the increase in body fat associated with obesity and the development of IR may activate SOD. However, it is important to note that this activation may not occur immediately in response to these conditions. Similarly, lower levels of SOD in women with PCOS compared to the control group has also been reported in another study[36]. These discrepant findings may be attributed to variations in the treatment approach and severity of the disease among the study population.

In this study, patients with PCOS exhibited significantly higher levels of lipid peroxidation compared to controls group. The observed increase in the lipid peroxidation could be attributed to the activation of GPx, which aims to mitigate the effects of heightened OS. However, it is crucial to consider and account for various confounding variables such as age, BMI, gravidity, blood vitamin E levels, and serum lipid levels when examining the impact of lipid peroxidation in women with PCOS. While it has been hypothesized that increased lipid peroxidation may be associated with PCOS in females, several studies[37] have failed to find significant changes in lipid peroxidation levels in relation to PCOS. Glutathione plays a key role in the hepatic ability to eliminate potentially harmful hydrophobic chemicals from the bloodstream and participate in the detoxification of electrophilic chemical compounds. These actions of glutathione contribute to the overall liver function and help maintain the body's detoxification processes.

Murri et al[14] conducted a meta-analysis and reported elevated levels of MDA in females with PCOS compared to the controls. Additionally, studies by Kuşçu et al[38] and Zhang et al[39] demonstrated increased MDA levels in PCOS patients, irrespective of obesity. Furthermore, Dursun et al[40] compared PCOS patients with matched controls in terms of BMI and smoking status, and found comparable serum MDA levels between the two groups. These findings highlight the association between PCOS and increased lipid peroxidation, as indicated by higher MDA levels, suggesting a potential role of OS in the pathogenesis of PCOS. A recent study[35] revealed a significant elevation in MDA values in patients diagnosed with PCOS compared to healthy controls. Interestingly, within the PCOS group, individuals with IR exhibited even higher MDA values compared to those without IR, and this association was independent of obesity. These findings suggest that increased OS, as indicated by elevated MDA levels, may be specifically linked to the presence of IR in PCOS patients, regardless of their body weight status. It has been reported that PCOS patients with a BMI greater than 40 kg/m^2 had significantly higher concentrations of MDA compared to women with normal BMI[41]. Hence, high levels of obesity, as indicated by an elevated BMI, may be associated with increased OS, as evidenced by higher MDA concentrations. These findings highlight the potential impact of excessive weight and obesity on oxidative damage in the body. In one study[31], a significant increase in MDA levels was observed in the obese group of patients with PCOS, indicating heightened OS associated with obesity. Additionally, in the nonobese PCOS group, oxidative stress was higher compared to the healthy group, and antioxidant levels were further decreased. In a separate study[42], elevated levels of MDA were observed in the group of individuals with PCOS compared to the control group.

Findings of the current study show that females with PCOS had significantly higher levels of serum homocysteine than the control group. These results are consistent with earlier research conducted by Salehpour et al[43], which also reported elevated homocysteine levels in patients with PCOS. In an endeavor to examine the association between homocysteine levels and PCOS, numerous studies[43] have been conducted utilizing BMI-matched patient cohorts. In line with these studies, our investigation focused on comparing homocysteine levels across subgroups defined

by BMI and waist circumference, encompassing both PCOS cases and control subjects. The collective evidence derived from these investigations has consistently revealed an elevation in homocysteine levels among individuals diagnosed with PCOS, thus corroborating earlier reports.

In patients with PCOS compared to control subjects, our analysis revealed increased antioxidant levels, and homocysteine levels, coupled with a significant increase in SOD and lipid peroxidation levels. Notably, these alterations were found to be independent of BMI, indicating that these parameters serve as unbiased determinants of the slightly elevated OS and increased homocysteine levels in PCOS patients[35].

In patients with PCOS, a positive correlation between MDA levels and several metabolic markers such as BMI, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), triglycerides, low-density lipoprotein (LDL) cholesterol, and insulin has been reported[31]. These findings highlight the significant relationship between increased OS, cardiovascular risk factors such as hypertension and endothelial dysfunction, and hyperinsulinemia detected through MDA levels in the patient group with PCOS[31].

Conclusions

Based on the findings of this study, it is concluded that women with PCOS exhibit higher serum concentrations of TG, GSH, SOD, lipid peroxidation, and homocysteine. Notably, these increments are more pronounced in individuals with higher BMI, advancing age, and duration of PCOS.

Ethics Approval

The ethical approval of the study was granted by Ethical Review Board, University of Science and Technology (U.S.T), College of Graduate Studies and Academic Advancement, Omdurman, Sudan (Reference No. J.A.T/K.A.M.T/M.A/2016).

Informed Consent

All study participants gave informed consent before filling out the questionnaire and collecting blood samples.

Authors' Contributions

A.H.A, S.E.O.H, A.M.A.B, A.E.A conceptualization, methodology development, and study design. H.A experimental execution. A.N.M, and T.Y.E.Y statistical analysis. H.O.E, T.A project supervision and coordination. M.S. conceptualization, writing- original draft and review. H.A.O., PK, and E.K. reviewed and edited the manuscript.

Availability of Data and Materials

The research data and materials used in this study will be made available upon request or as needed.

Conflict of Interest

The authors declare no conflict of interest.

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