İstanbul Med J 2022; 23(2): 90–5
DOI: 10.4274/imj.galenos.2022.28445

Impact of Copper and Oxidative Stress Index Levels on Insulin Resistance, Lipid Profile and Hormonal Status of Patients with Polycystic Ovary Syndrome

Nil Atakul[1], Şahabettin Selek[2], Fatmanur Yılmaz Köktaşoğlu[2], Berna Şermin Kılıç[1], Ayşe Zehra Gül[2], Yıldız Atamer[3]

[1]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
[2]Bezmialem Vakıf University Faculty of Medicine, Department of Medical Biochemistry, İstanbul, Turkey
[3]Beykent University Faculty of Medicine, Department of Medical Biochemistry, İstanbul, Turkey

ABSTRACT

Introduction: Polycystic ovary syndrome (PCOS) is one of the most common endocrine abnormalities of reproductive age and has a highly heterogeneous nature regarding its multisystemic symptoms. To elicit pathophysiological roots, metabolic mapping and between-correlations among key parameters are of vital importance. We generated a platform including cardinal hormones, lipids, homeostasis model assessment of insulin resistance (HOMA-IR) and oxidative markers [total-oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), copper (Cu)] related to pathophysiology.

Methods: This prospective case-control study included 46 patients with PCOS and 44 non-PCOS healthy women. Samples were obtained from the Obstetrics and Gynecology Clinic of University of Health Sciences Turkey, İstanbul Training and Research Hospital. TAS, TOS, and Cu levels were measured by automated methods.

Results: Anti-Mullerian hormone, total testosterone (TT), dehydroepiandrosterone sulfate, low-density lipoprotein, high-density lipoprotein (HDL), total cholesterol, TOS, OSI were increased in patients with PCOS with no significant differences in the mean values of other parameters. ROC analysis revealed that TOS and OSI had an acceptable predictive value for PCOS diagnosis. Plasma HOMA-IR, triglyceride, HDL, TT, and sex-hormone-binding globulin levels were correlated with OS markers.

Conclusion: Redox status was found to be sensitive to hormonal alterations. Metabolites were then were compared with the oxidative markers to reveal any relationship that may explain the causal link between metabolic and redox changes Ultimately, evaluating broad-based metabolic profiling of patients, the current study contributes to the literature, which has controversial data and correlation findings poses new questions requiring further research to elicit underlying mechanisms and so to set new targets for both prevention and treatment.

Keywords: Polycystic ovary syndrome, copper, oxidative stress, testosterone

Introduction

The most frequent endocrine disorder of reproductive age, polycystic ovary syndrome (PCOS), manifests with multisystemic symptoms associated with increasing incidence of obesity, metabolic syndrome, and diabetes in the young population. Much efforts have been made since then search for early indications of PCOS to avoid future complications before onset.

Like many complex pathologies in which both environmental and genetic factors interact in the etiology, PCOS has been associated with imbalanced redox status (1). Thus, oxidative stress (OS) holds great promise in understanding pathological processes and practical use as a therapeutic target. Earlier reports showed that insulin resistance (IR) is the central contributing factor that may originate from increased oxidative stress, leading to PCOS progression. Other factors have been described as obesity and abdominal adiposity (1). It has been shown that serum oxidative markers, such as homocysteine, malondialdehyde, and superoxide dismutase activity, were higher while glutathione was lower in patients with PCOS (1). The current study will test the total oxidant status (TOS)-total antioxidant status (TAS) and serum copper (Cu) levels and calculated the oxidative stress index (OSI) as indicators of the serum oxidative status of the participants. Enzymes that are involved in many biological mechanisms are an integral part of Cu, and Cu levels play a crucial role in the process of oxidative enzymes (cytochrome c oxidase, superoxide dismutase, ascorbate oxidase) (2). Only a few studies have investigated serum Cu levels in patients with PCOS (3-7). A recent meta-

Address for Correspondence: Nil Atakul MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
Phone: +90 532 241 31 52 **E-mail:** nil_atakul@yahoo.com **ORCID ID:** orcid.org/0000-0003-3874-8797

Cite this article as: Atakul N, Selek Ş, Yılmaz Köktaşoğlu F, Kılıç BŞ, Gül AZ, Atamer Y. Impact of Copper and Oxidative Stress Index Levels on Insulin Resistance, Lipid Profile and Hormonal Status of Patients with Polycystic Ovary Syndrome. İstanbul Med J 2022; 23(2): 90-5.

Received: 01.12.2021
Accepted: 01.04.2022

analysis reported that Cu in patients with PCOS was higher than healthy and PCOS women with IR (8). To our knowledge, the correlation of Cu levels with hormonal levels in patients with PCOS was studied only in one study (5), with no studies regarding its correlation with lipid parameters.

Correlation of hormonal levels in PCOS with OS markers was studied only in several studies (9-11) with inconclusive results. Our work will contribute to the literature showing new evidence on serum hormone levels and possible correlations with investigated oxidative markers), implying their etiological role in PCOS development.

Ultimately, this study showed new evidence on the serum levels of a specific hormone, lipid, and OS markers related to the pathophysiology of PCOS. Metabolic parameters will then be compared with oxidative markers to reveal any relationship that may explain the causal link between metabolic and redox changes. involving a set of parameters reflecting functions, our work will also contribute to the integrated understanding of PCOS.

Methods

A minimum number of 40 individuals were required for each group (given the effect size of 0.60 and p-value of 0.05), adjusting the 80% level in power analysis.

This prospective case-control study included 46 patients with PCOS and 44 non-PCOS healthy women aged between 18 and 43. Participants applying to the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Gynaecology and Obstetrics were selected from October 2020 to January 2021, and PCOS diagnosis was made in compliance with the Rotterdam criteria (12). The control group of 44 healthy, reproductive-aged women who voluntarily joined our study was recruited upon admission to our outpatient clinic for routine gynecologic examination. The control group body mass index (BMI) and age were matched to patients with PCOS in our study. All the control patients were selected from non-PCOS patients who were thoroughly examined before inclusion in the study. The serum levels of anti-Mullerian hormone (AMH), total testosterone (TT), follicle-stimulating hormone (FSH), luteinizing hormone (LH), dehydroepiandrosterone sulfate (DHEA-SO4), prolactin (PRL), thyroid-stimulating hormone (TSH), and lipid parameters [total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG)], were investigated with OS markers (TOS, TAS, Cu, OSI) and compared between the two groups.

The study was conducted under the Declaration of Helsinki and was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2515, date: 18.09.2020). Each participant gave written consent.

Inclusion Criteria

Patients who met the following two or three criteria were selected: oligo/anovulation, hyperandrogenism (HA) (clinical/biochemical), and polycystic ovaries on ultrasound. All individuals were 18-43-year-old women, and serum samples were collected during their first visit (after a confirmed PCOS diagnosis for patients and, if not, for controls).

Exclusion Criteria

Exclusion criteria for both the PCOS and control groups included pregnancy, congenital adrenal hyperplasia, adrenal/ovarian tumors, diabetes mellitus, hyperprolactinemia, hypothyroidism, Cushing disease, and oral contraceptive use hypogonadotropic hypogonadism. Individuals with chronic diseases (including cardiovascular-renal diseases), malignancies, active infection, and regular drug/alcohol/cigarette usage were also excluded from the study.

Forty-six patients with PCOS and 44 controls who matched for BMI and age were included in the study. Samples were obtained from the Obstetrics and Gynecology Clinic of University of Health Sciences Turkey, İstanbul Training and Research Hospital. Morning venous blood samples were obtained between 9 and 10 am between days 3 and 5 of the menstrual cycle; after centrifugation at 2000-3000 rpm at 4 °C for 20 min, serum samples were separated and frozen at -80 °C until assayed. The serum, TAS, TOS, and Cu levels were measured by automated methods.

Determination of Hormone and Lipid Levels

Hormone levels and lipid markers were analyzed in the biochemistry laboratory. LH, FSH, TT, DHEAS, PRL, and TSH serum levels were assessed using a UniCel DxI800 analyzer (Beckman Coulter, Brea, CA) immunoenzymatically. AMH levels were measured using the electrochemiluminescence immunoassay method (Roche-Cobas E411, Roche Diagnostics, Mannheim, Germany). Metabolic and lipid profiles (fasting glucose, HDL, LDL, TC and TG) were determined via spectrophotometric analysis [Beckman Coulter AU 5800 analyzer, Beckman Coulter, Brea, CA (Abbott Diagnostics, USA)]. Homeostasis model assessment of insulin resistance (HOMA-IR)=fasting blood glucose (mmol/L) x fasting blood plasma insulin (mU/mL)/22.5.

Determination of TAS

From Erel's (13) method, fully automatic colorimetry was used for serum TAS-level measurement (analysis done with Abbott ARCHITECT c8000 clinical chemistry analyzer). Measuring the number of OH-radicals is the principle of the Erel method. To produce the OH-radical, o-Diasidine ferrous ion with H_2O_2 had a Fenton-type chemical reaction, and a change in the color occurs. Changes in color could be prevented by neutralization of oxidants with serum antioxidants. Oxidative free radical reactions induced by OH-, determined the antioxidant capacity by this method. An alpha-tocopherol analog Trolox was used for this method.

Trolox equivalent, mmol/L given in the results. The method sensitivity is 3%.

Determination of TOS

Another method by Erel (14), used for measuring serum TOS levels by fully automatic photometry Erel (14) (analysis done with an Abbott ARCHITECT c8000 clinical chemistry analyzer. The oxidization of o-dianisidine ferrous ions to ferric ions was the principle of this method. The xylenol orange induced color changes are visualized as oxidation of ferric ions in an acidic environment. The number of oxidants in the serum is correlated with the color density. H_2O_2 is the standard method. H_2O_2 equivalent, µmol/L given in the results. The metsensitivityvity is 2%.

Calculation of OSI

The OSI (arbitrary unit)=TOS (μmol H_2O_2 Eq/L)/10×TAS (mmol Trolox Eq/L).

Determination of Serum Cu levels

The available Rel Assay Cu measurement kit (Gaziantep, Turkey) was used for serum Cu measurements by full photometry (c8000 Abbott ARCHITECT clinical chemistry analyzers). The color change of DiBr-PAESA from red-orange to violet in an alkaline environment is proportional to Cu levels in samples (μg/dL). The red-orange DiBr-PAESA conversion to violet by the alkaline environment is proportional to Cu levels in the sample (μg/dL). Cu sulfate absorbance changes were measured at around 572 mm.

Statistical Analysis

G Power software was used to calculate the study's sample size (2021, Heinrich-Heine-University, Düsseldorf). The Shapiro-Wilk test was applied to assess data distributions, and the data were normally distributed (p≥0.05). Group differences were defined using an independent sample t-test. The results are shown as the mean ± standard deviation, and p=0.05 was set as the level of statistical significance. Correlation analysis was carried out for each group. Receiver operating characteristic curve (ROC) analysis was performed to define the discrimination ability of the investigated serum parameters for PCOS. Discriminant analysis was performed to determine the prediction capacity of the parameters for PCOS. Analyses were performed with IBM SPSS version 27.0 software (IBM Corporation, Armonk, NY, USA).

Results

Demographic and clinical data are shown in Table 1. No differences in age or BMI were observed between the groups (p>0.05).

Significantly higher levels of AMH, TT, DHEAS, LDL, HDL, TC, TOS, and OSI and significantly lower levels of FSH were recorded in patients with PCOS (p<0.05). There was no significant difference in the mean values of LH, PRL, TSH, TG, Cu, and TAS (Table 1).

As an essential parameter for PCOS, the LH/FSH ratio appeared to have a strong positive association with TT, a moderate positive correlation with TGs and a moderate negative correlation with HDL levels (r=0.65, p=0.009, r=0.48, p=0.028, r=-0.46, p=0.024, Table 2). In patients with PCOS, TOS showed a strong positive correlation with OSI and Cu and a moderate correlation with HOMA-IR (r=0.94, p=0.001, r=0.59, p=0.023, r=0.40, p=0.011, Table 2). The mean HOMA-IR value was 2.79±2.06 in patients with PCOS.

Cu levels were strongly correlated with TOS, OSI and sex-hormone binding globulin (SHBG) (r=0.59, p=0.023, r=0.59, p=0.001, r=0.59, p=0.004, Table 2).

TAS was correlated with TT and HOMA-IR (r=0.47, p=0.023, r=0.53, p=0.001). Additionally, FSH was moderately correlated with AMH in the PCOS group (r=0.46, p=0.035, Table 2).

Investigating lipid profile associations with TGs showed a moderate positive correlation with the LH/FSH ratio and LH value in patients with PCOS (r=0.48, p=0.028, r=0.47, p=0.023), and HDL was negatively related to the LH/FSH ratio and TT (r=-0.54, p=0.012, r=-0.46, p=0.024 Table 2).

Table 1. Demographic and clinical data of the study population

	Control	PCOS	p value
Age (year)	24.7±5.4	22.8±5.4	ns
BMI (kg/m²)	24.3±3.4	25.6±6.5	ns
Fasting glucose (mg/dL)	89.4±8.3	89.8±9.5	ns
AMH (ng/mL)	3.9±3.3	8.5±2.3	0.001***
FSH (mIU/mL)	8.9±1.1	8.2±0.9	0.01**
LH (mIU/mL)	7.8±1.1	7.8±1.9	ns
TT (ng/dL)	46.7±1.2	52.7±5	0.001***
PRL (μg/L)	10.9±1.8	10.8±2.3	ns
DHEAS (μg/dL)	205.4±8.8	234.8±23.2	0.001***
TSH (ng/mL)	1.7±1.2	1.8±0.9	ns
TC (mIU/mL)	146.8±6.5	174.1±26.5	0.001***
TG (mg/dL)	89.1±23.1	80.5±32.4	ns
LDL (mg/dL)	84.8±10.2	112.5±28.2	0.001***
HDL (mIU/mL)	42.2±2.7	50.7±9.1	0.001***
TAS (mmol Trolox Eq/L)	1.5±0.1	1.5±0.2	ns
TOS (μmol H_2O_2 Eq/L)	3.4±0.7	4.5±1.6	0.001***
OSI (arbitrary unit)	0.2	0.3±0.1	0.001***
Cu^{2+} (μg/dL)	117.61±32.55	123.77±46.95	ns

***p<0.001 level of significance. Values are described as mean ± standard deviation (ns: non-significant; *0.01<p<0.05; **0.001<p<0.01; ***p<0.001 level of significance). BMI: Body mass index, AMH: Anti-Mullerian hormone, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, TT: Total testosterone, PRL: Prolactin, DHEA-SO4: Dehydroepiandrosterone sulfate, TSH: Thyroid-stimulating hormone, TC: Total cholesterol, TG: Total triglyceride HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, Cu: Copper

The free androgen index (FAI) was calculated as TT/SHBG and obtained only for patients with PCOS (since only patients with PCOS had SHBG values). FAI displayed no significant correlation with any marker.

According to ROC analysis, significant results were obtained for TOS and OSI parameters (Figure 1). OSI had an AUC value of 0.68, and OSI had an AUC value of 0.69 (acceptable diagnostic ability) (Table 3).

None of our OS markers were different according to BMI in patients with PCOS. TOS, TAS, OSI and Cu levels were statistically insignificant in patients with BMI <25 kg/m² and BMI ≥25 kg/m² (p=0.104, p=0.094, p=0.174, p=0.952 respectively).

TOS and TAS levels were significantly higher in patients with PCOS with HOMA-IR ≥2 (p=0.045, p=0.021 respectively). TOS levels were 5,19 μmol H_2O_2 Eq/L. TAS levels were 1.54 mmol Trolox Eq/L in patients with PCOS with HOMA-IR ≥2. Cu and OSI levels were statistically insignificant between patients according to HOMA-IR values (p=0.449, p=0.152 respectively).

Discussion

In our study, multiple hormone and metabolic parameters were investigated with OS markers TOS and OSI, which were higher in the PCOS group as expected, whereas TAS and Cu levels were not different

Table 2. The correlation table displays the significant associations obtained in the PCOS

Pearson correlation	FSH (mIU/mL)	LH (mIU/mL)	TT (ng/dL)	LH/FSH	OSI (arbitrary unit)	Cu $^{2+}$ (µg/dL)	HOMA-IR	p value
AMH (ng/mL)	0.46*							0.035
LH/FSH			0.65**					0.009
TAS (mmol Trolox Eq/L)			0.47*				0.53**	0.023 0.001
BMI (kg/m^2)		0.52**		0.45*				0.011 0.041
TC (mIU/mL)								
TG (mg/dL)		0.47*		0.48*				0.025 0.028
LDL (mIU/mL)								
HDL (mIU/mL)			-0.46*	-0.54**				0.024 0.012
TOS (µmol H_2O_2 Eq/L)					0.94**	0.59**	0.40	0.000 0.023 0.011
OSI (arbitrary unit)						0.59**		0.000
SHBG (nmol/L)						0.59**		0.004

**Correlation was significant at the 0.01 level (2-tailed). *Correlation was significant at the 0.05 level (2-tailed). AMH: Anti-Mullerian hormone, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, BMI: Body mass index, TC: Total cholesterol, TG: Total triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, SHBG: Sex-hormone-binding globulin

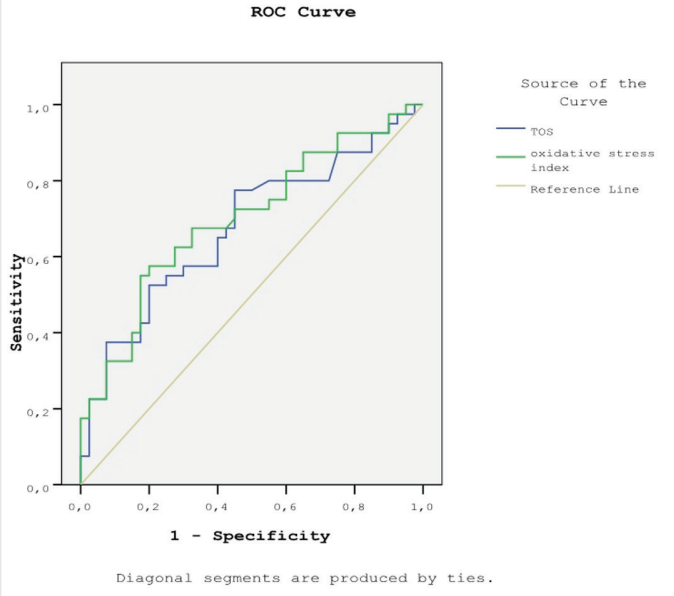

Figure 1. The ROC curve analysis for predicting PCOS. The blue line represents TOS; the green line represents OSI
ROC: Receiver operating characteristic, PCOS: Polycystic ovary syndrome, TOS: Total oxidant status, OSI: Oxidative stress index

between the groups. A discriminant analysis with TOS and OSI values detected PCOS with acceptable diagnostic ability. The direct correlation between OS markers and plasma HOMA-IR, TG, HDL, TT, or SHBG levels suggest that metabolic imbalance and hormonal disturbance contribute to increased oxidative status.

Despite not being adequate for predicting separately, the LH/FSH ratio may show accordance with specific metabolic characteristics of PCOS. One study showed that a high LH/FSH ratio was related to insulin, TT, and AMH levels in a subgroup of patients with PCOS (15). Our results showed that patients PCOS had a strong correlation between the LH/FSH ratio and TT. This may explain the causal relationship of TT secretion with LH levels and contribute to the common understanding of PCOS pathophysiology. Interestingly, the PCOS group LH/FSH ratio also positively correlated with TGs and BMI and a negative correlation with HDL. In a recent study, fasting vs random PCOS blood analysis showed low levels of TC and LH levels in fasting but no difference in LH/FSH levels (16). All these relationships may provide insight into PCOS physiology and help interpret PCOS metabolism with an integral approach. The impaired correlation between OS markers and the LH/FSH ratio in the PCOS group seems to indicate that serum hormone alterations occur independently of OS. Here, enhanced OS seems more of a result of metabolic imbalance rather than being an etiological factor. Previous research supported this hypothesis by claiming that PCOS-related OS does not directly on the hormone profile in PCOS and would likely result from metabolic perturbations such as IR, dyslipidemia and obesity (17).

HA is one of the main characteristics of the disease and indicates that PCOS after other causes of HA have been ruled out. Eliciting the pathophysiological role of the circulating androgenic hormones that lead to HA setting is of prime importance. The correlation analysis of DHEAS in one study of patients with PCOS showed no relationship with fasting glucose, lipids, or pathogenesis-related hormones, supporting the that DHEAS independently increases the metabolic alteration seen in PCOS (18).

TT levels were positively correlated with TAS levels in patients with PCOS. İncreased TAS activity and its association with TT and HOMA-IR suggest

Table 3. PCOS discrimination analysis with TOS and OSI parameters

	Diagnostic test					ROC curve		p
	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	95% CI	
OSI	**≥2.5**	63.0	73.0	68.6	64.4	**0.69**	0.584-0.814	**0.002****
TOS	**≥3.17**	78.0	55.0	62.5	68.8	**0.68**	0.557-0.795	**0.007****

*PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval, **Receiver operating characteristic curve analysis test, AUC: Area under the curve, OSI: Oxidative stress index, TOS: Total oxidant status

that TAS activity contributes to HA and IR and vice versa, increasing the risk of atherogenesis.

To assess HA status more accurately in females, it is also suggested to include FAI (19). Few studies have investigated FAI levels and correlations with metabolic parameters in patients with PCOS (20-22). To the best of our knowledge, the correlation of FAI levels with markers of OS was not investigated in the population with PCOS. The FAI is a ratio of TT to SHBG (same units), and an indicator of physiologically active testosterone. One study found higher levels of FAI in overweight patients (BMI ≥27) with positive correlations of FAI with glycemia, HOMA-IR, TG, TC, and a negative relation with HDL cholesterol. This suggests that FAI-FT can be used for tract poor cardiometabolic outcomes in the population with PCOS (20). In another study, low FAI levels were associated with higher TC and HDL levels only in lean patients (21). FAI values did not correlate with BMI or any metabolic or OS parameters investigated in our study. Further studies are required to explore these associations.

Regarding other metabolic indicators, fasting glucose was not different between the groups, our findings regarding hormone and OS marker levels in the two groups were evaluated independently from the effect of IR. In this study, HOMA-IR <2 levels were associated with low TAS and TOS levels in PCOS, but no correlation of OS marker levels with BMI was found. The correlation of IR with OS markers has been reported in a few studies. Low levels of OS in patients with PCOS were found in patients with normal IR and low BMI PCOS (23,24). The lack of correlation of OS markers with BMI might produce distinctive and intrinsic defects in insulin secretion in patients with PCOS independent of obesity.

The correlation of testosterone levels with lipid parameters in PCOS shows that the lipid profile was less severely impaired in patients without HA than in those with HA (11,21). Also, HDL levels in our study were negatively correlated with TT. The TG levels were positively related to LH/FSH in patients, which may be value for indicate that LH secretion in PCOS might be related mainly to metabolic disturbances and atherogenesis and that high testosterone levels is secondary to the androgenic response to high LH levels in patients. Globally, the literature has many contrary results about the dyslipidemia patterns of PCOS. A study found that decreased HDL levels with increased TG and LDL in patients (25). Others reported similar HDL and LDL levels while showing a reduced capacity for cholesterol efflux and lipid particle atherogenic pattern and size in patients (VLDL and LDL) (26). Although each patient has a different lipid profile, previous and current findings may underline the enhanced risk of future cardiovascular complications in the population with PCOS. The fact that interfering factors highly influence lipid parameters makes it difficult to make the exact assumptions on the issue. Thus, further research adjusting these factors and including a larger sample size should be conducted to confirm the results.

In our study, trace element Cu levels correlated with TOS, OSI, and SHBG levels in PCOS, and levels were not significantly different from controls. Studies have focused mainly on Cu levels between PCOS and control groups, with sparse reports about its effects on metabolic and hormonal disturbances. In a recent meta-analysis, serum Cu-level prediction of PCOS was not statistically significant but in patients with PCOS with IR, Cu serum levels were higher than non-PCOS patients (8). Zheng et al. (5) reported that each 1-µg/L increase in Cu levels was associated with a change in reproductive hormone levels (LH, testosterone, fasting insulin, and TG), and they assumed that Cu might play a role in the pathogenesis of PCOS related to reproductive hormone levels. Although we found a correlation of Cu levels only with SHBG levels in PCOS, a strong correlation with OS markers showed that chronic Cu overload may have a negative effect on redox status in PCOS by prooxidant and oxidant mechanisms.

Our current study found that the oxidative markers TOS and OSI levels were significantly higher in PCOS than non-PCOS, while TAS values were not statistically different between PCOS and non-PCOS. TOS and TAS elevations were previously recorded for PCOS (19), and OSI was also reported to increase in previous works (23). The findings of a study essentially correspond to the current study and support our results with increased TOS and OSI with no difference in TAS levels (23). In a more recent study, serum OSI, TAS, and TOS levels were significantly different in the PCOS group than in the control group (27). OSI levels were investigated in patients with PCOS only recently (11,23,27-29), and our study is the first to provide a cut-off value for PCOS detection. With these and current findings, we conclude that OS markers are increased in PCOS, showing the imbalanced redox homeostasis of patients.

Study Limitations

Although each patient has a different lipid profile, previous and current findings may underline the enhanced risk of future cardiovascular complications in the population with PCOS. The fact that lipid parameters are highly influenced by interfering factors makes it difficult the exact assumptions on the issue. Thus, further research adjusting these factors and including a larger sample size should be conducted to verify the discussed results.

Conclusion

Essential hormone levels with lipid profiles and oxidative status of patients were evaluated, offering new evidence to this literature. Discussing the place of OS in PCOS, our premise is that rather than playing a primary role in the initial steps of pathophysiology, OS occurs more likely because of HA or IR. With the correlation findings among

hormone levels and oxidative markers, we pose new questions requiring further research to elicit underlying mechanisms and set new targets for prevention and treatment. The association of Cu and OS marker levels with clinical and laboratory findings suggest that these factors taken together are involved in aggravating the proinflammatory status in women with PCOS.

Ethics Committee Approval: The study was conducted under the Declaration of Helsinki and was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2515, date: 18.09.2020).

Informed Consent: Each participant gave written consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - N.A., Ş.S., F.Y.K., B.Ş.K., A.Z.G., Concept - N.A., Ş.S., Y.A.; Design - N.A., Ş.S., Y.A.; Data Collection or Processing - B.Ş.K., A.Z.G., Y.A.; Analysis or Interpretation - N.A., Ş.S., B.Ş.K.; Literature Search - N.A., A.Z.G., Y.A.; Writing - N.A., F.Y.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Murri M, Luque-Ramírez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF. Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysis. Hum Reprod Update 2013; 19: 268-88.
2. Valko M, Morris H, Cronin MT. Metals, toxicity and oxidative stress. Curr Med Chem 2005; 2: 1161-208.
3. Kanafchian M, Esmaeilzadeh S, Mahjoub S, Rahsepar M, Ghasemi M. Status of Serum Copper, Magnesium, and Total Antioxidant Capacity in Patients with Polycystic Ovary Syndrome. Biol Trace Elem Res 2020; 193: 111-7.
4. Celik C, Bastu E, Abali R, Alpsoy S, Guzel EC, Aydemir B, et al. The relationship between copper, homocysteine and early vascular disease in lean women with polycystic ovary syndrome. Gynecol Endocrinol 2013; 29: 488-91.
5. Zheng G, Wang L, Guo Z, Sun L, Wang L, Wang C, et al. Association of Serum Heavy Metals and Trace Element Concentrations with Reproductive Hormone Levels and Polycystic Ovary Syndrome in a Chinese Population. Biol Trace Elem Res 2015; 167: 1-10.
6. Bizoń A, Słowiak A, Franik G, Biernacka-Bartnik A, Madej P. Zinc, copper, sirtuin 1 concentration, and glucose metabolism parameters in the blood of women with polycystic ovary syndrome. Gynecol Endocrinol 2020; 36: 951-4.
7. Revathi R, Julius A, Singaravelu S. Correlation of serum copper, zinc, magnesium with insulin resistance in PCOS female of reproductive age group. Int J Pharm Res 2018; 10: 789-92.
8. Yin J, Hong X, Ma J, Bu Y, Liu R. Serum Trace Elements in Patients With Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne) 2020; 11: 572384.
9. Hilali N, Vural M, Camuzcuoglu H, Camuzcuoglu A. Increased prolidase activity and oxidative stress in PCOS. Clin Endocrinol 2013; 79: 105-10.
10. Beyazit F, Yilmaz N, Balci O, Adam M, Yaman ST. Evaluation of Oxidative Stress in Women with Polycystic Ovarian Syndrome as Represented by Serum Ischemia Modified Albumin and Its Correlation with Testosterone and Insulin Resistance. Intern Med 2016; 55: 2359-64.
11. Zhang R, Liu H, Bai H Liu Q, Guan L, Fan P. Oxidative stress status in Chinese women with different clinical phenotypes of polycystic ovary syndrome. Clin Endocrinol (Oxf) 2017; 86: 88-96.
12. Lizneva D, Suturina L, Walker W, Brakta S, Brakta S, Gavrilova-Jordan L, et al. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril 2016; 106: 6-15.
13. Erel O. A novel automated direct measurement method for total antioxidant capacity using a new generation, more stable ABTS radical cation. Clin Biochem 2004; 37: 277-85.
14. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem 2005; 38: 1103-11.
15. Malini NA, Roy George K. Evaluation of different ranges of LH:FSH ratios in polycystic ovarian syndrome (PCOS) - Clinical based case control study. Gen Comp Endocrinol 2018; 260: 51-7.
16. Arshad FA, Mehmood R, Kausar N, Bibi A, Khan MA, Hussain S, et al. Assessment and association between lipid and hormonal profile in nonpregnant females having polycystic ovarian syndrome. Endocrinol Metab Syndr 2019; 8: 1-5.
17. Macut D, Bjekić-Macut J, Savić-Radojević A. Dyslipidemia and oxidative stress in PCOS. Front Horm Res 2013; 40: 51-63.
18. Paschou SA, Palioura E, Ioannidis D, Anagnostis P, Panagiotakou A, Loi V, et al. Adrenal hyperandrogenism does not deteriorate insulin resistance and lipid profile in women with PCOS. Endocr Connect 2017 ;6: 601-6.
19. Verit FF, Erel O. Oxidative stress in nonobese women with polycystic ovary syndrome: correlations with endocrine and screening parameters. Gynecol Obstet Invest 2008; 65: 233-9.
20. Lazúrová I, Lazúrová Z, Figurová J, Ujházi S, Dravecká I, Mašlanková J, et al. Relationship between steroid hormones and metabolic profile in women with polycystic ovary syndrome. Physiol Res 2019; 68: 457-65.
21. Spałkowska M, Mrozińska S, Gałuszka-Bednarczyk A, Gosztyła K, Przywara A, Guzik J, et al. The PCOS Patients differ in Lipid Profile According to their Phenotypes. Exp Clin Endocrin Diabetes 2018; 126: 437-44.
22. Li R, Yu G, Yang D, Li S, Lu S, Wu X, et al. Prevalence and predictors of metabolic abnormalities in Chinese women with PCOS: a cross- sectional study. BMC Endocr Disord 2014; 14: 76.
23. Torun AN, Vural M, Cece H, Camuzcuoglu H, Toy H, Aksoy N. Paraoxonase-1 is not affected in polycystic ovary syndrome without metabolic syndrome and insulin resistance, but oxidative stress is altered. Gynecol Endocrinol 2011; 27: 988-92.
24. Cakir E, Ozbek M, Ozkaya E, Colak N, Cakal E, Sayki M, et al. Oxidative stress markers are not valuable markers in lean and early age of polycystic ovary syndrome patients. J Endocrinol Invest 2011; 34: e178-e82.
25. Kiranmayee D, Kavya K, Himabindu Y, Sriharibabu M, Madhuri GLJ, Venu S. Correlations between anthropometry and lipid profile in women with PCOS. J Hum Reprod Sci 2017; 10: 167-72.
26. Roe A, Hillman J, Butts S, Smith M, Rader D, Playford M, et al. Decreased cholesterol efflux capacity and atherogenic lipid profile in young women with PCOS. J Clin Endocrinol Metab 2014; 99: E841-E7.
27. Kirmizi DA, Baser E, Turksoy VA, Kara M, Yalvac ES, Gocmen AY. Are Heavy Metal Exposure and Trace Element Levels Related to Metabolic and Endocrine Problems in Polycystic Ovary Syndrome?. Biol Trace Elem Res 2020; 198: 77-86.
28. Sak S, Uyanikoglu H, Incebiyik A, Incebiyik H, Hilali NG, Sabuncu T, et al. Associations of serum fetuin-A and oxidative stress parameters with polycystic ovary syndrome. Clin Exp Reprod Med 2018; 45: 116-21.
29. Uyanikoglu H, Sabuncu T, Dursun H, Sezen H, Aksoy N. Circulating levels of apoptotic markers and oxidative stress parameters in women with polycystic ovary syndrome: a case-controlled descriptive study. Biomarkers 2017; 22: 643-7.