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Polycystic Ovary Syndrome and Oxidative Stress

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ABSTRACT

Objective: In reproductive age, polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women. Although it is a very common, pathogenesis is still unclear. Oxidative stress is one of the proposed mechanisms. In our study, we aimed to evaluate the clinical and laboratory findings and oxidative stress parameters in PCOS. Methods: In our prospective study, we included 75 PCOS patients, diagnosed according to the Rotterdam criteria, and 75 healthy people as the control group. Participants' demographic data and menstrual cycle patterns were questioned. Lipid profile and insulin resistance were examined. Ferriman-Gallwey scoring and androgen levels were studied to evaluate hirsutism. Superoxide dismutase (SOD), catalase and urotensin-2, which are oxidative stress markers, were measured Results: The average age of the PCOS group was 23.1 and the control group was 27. Menstrual cycle duration was 47.9 versus 27.5 in the PCOS ($p<0.05$). Ferriman-Gallwey score was significantly higher in the PCOS group ($p<0.05$). There was a worse lipid profile in the control group ($p>0.05$). In our study, SOD, catalase and urotensin-2 levels were measured to evaluate oxidative stress. All three parameters were found to be higher in the PCOS group (for catalase and urotensin 2 $p<0.05$; for SOD $p>0.05$). Conclusion: PCOS is a group of syndromes whose etiology is still unclear. It has a wide variety of clinical and laboratory findings. Oxidative stress is one of the theories put forward in pathogenesis.

Key words: Insulin Resistance, Polycystic Ovary Syndrome, Oxidative Stress.

Polikistik Over Sendromu ve Oksidatif Stres

ÖZ

Amaç: Reprodüktif dönemdeki kadınlarda polikistik over sendromu (PCOS) en sık görülen endokrin bozukluklarından birisidir. Çok yaygın olmasına rağmen patogenezi halen belirsizdir. Oksidatif stres öne sürülen mekanizmalardan birisidir. Çalışmamızda PCOS hastalarındaki klinik ve labaratuar bulgularını ve oksidatif stres parametrelerini değerlendirmeyi amaçladık. Yöntem: Prospektif olan çalışmamıza Rotterdam kriterlerine göre tanısı konulmuş 75 PCOS hastası ve kontrol grubu olarak 75 sağlıklı kişileri aldık. Katılımcıların demografik verileri ve menstrüel siklus düzeni sorgulandı. Lipid profili, insulin direncine bakıldı. Hirsutizm değerlendirmesi için Ferriman-Gallwey skorlaması ve androjen düzeyleri çalışıldı. Oksidatif stres belirteçlerinden süperoksit dismutaz (SOD), katalaz ve urotensin-2 bakıldı. Bulgular: PCOS grubunun yaş ortalaması 23.1 kontrol grubunun ise 27 olarak saptandı. PCOS grubunda 47.9 olan menstrüel siklus süresi kontrol grubunda 27.5 olarak bulundu ($p<0,05$). Ferriman-Gallwey skoru PCOS grubunda daha yüksekti ($p<0.05$). Lipid profili değerlendirildiğinde anlamlı olmamakla birlikte kontrol grubunda daha kötü bir lipid profili mevcuttu. Çalışmamızda oksidatif stresi değerlendirmek için SOD, katalaz ve urotensin-2 düzeyleri çalışıldı. Her üç parametrede PCOS grubunda daha yüksek saptandı katalaz ve ürotensin için $p<0.05$; SOD için $p>0.05$). Sonuç: PCOS etiyolojisi halen net ortaya konulamamış sendromlar grubudur. Çok çeşitli klinik ve laboratuvar bulguları vardır. Oksidatif stres patogenezde öne sürülen teorilerden birisidir.

Anahtar kelimeler: İnsulin Direnci, Polikistik Over Sendromu, Oksidatif Stres.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) affects approximately 5-10% of women of reproductive age and is one of the most common endocrinological disorders in this age group. (Escobar et al. 2018). Affected individuals show signs of hyperandrogenism with anovulation or oligoovulation, and this causes disorders in the reproductive, endocrinological and psychological state of the person (Wekker et al. 2020). Today, the Rotterdam criteria published in 2003 are used for diagnosis. According to these criteria, two of the following three criteria must be met: a) oligo or anovulation; b) clinical and/or biochemical signs of hyperandrogenism; c) Polycystic ovaries on ultrasound. Moreover, symptoms such as Cushing's or congenital adrenal hyperplasia, which may cause hyperandrogenism, should be excluded (Rotterdam ESHRE/ASRM 2003).

The clinical manifestation of PCOS is highly variable. Infertility due to chronic anovulation, endocrinological disorders such as insulin resistance, obesity, dyslipidemia; symptoms such as hirsutism, acne caused by hyperandrogenism. It has a very variable clinical spectrum, including menstrual disorders and an increase in long-term estrogen-dependent cancers due to unopposed estrogen (Yin et al. 2019; Gunninget al. 2020; Risal et al. 2019).

The mechanism and pathogenesis of PCOS development is still not clearly understood. Today, it is believed to occur as a result of the interaction of genetic factors and environmental factors (Stener-Victorin et al. 2021). The disease is a heterogeneous disease. A three-dimensional model is emphasized to explain etiology. According to this model, the disease is multifactorial, multipathway and multilevel that explains the heterogenity of the disease (Escobar et al. 2018).

An imbalance between oxidants and antioxidants in the body is defined as oxidative stress. Oxidants (also known as free radicals) are highly reactive molecules. They stabilize by stealing electrons from antioxidants (Kurutas et al. 2016). Accumulation of active oxidative substances in the body causes cell dysfunction. This situation is the result of protein and DNA damage and lipid peroxidation(Lu et al. 2018). Oxidants can be divided into two main groups: Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). Examples of ROS are superoxide anion ($O2^-$), hydrogen peroxide (H2O2) and hydroxyl (OH). There are two main sources of ROS in the body. The primary source is oxidative phosphorylation occurring in mitochondria. They arise secondarily as the end product of cytochrome p450 enzyme and activated inflammatory cells (Allen et al. 2000). RNS contains nitrogen dioxide (NO2) and nitric oxide (NO) (Di Meo et al. 2016). Free oxygen radicals can also occur with environmental factors. Examples of these are ionizing radiation or pollution in the atmosphere (Valko et al. 2005). ROS and RNS have variable effects on cells depending on their amount. At low and moderate levels, these oxidants participate in physiological functions such as being part of the anti-inflammatory process in the body (Sies et al. 2020). However, if these oxidatives are in excessive amounts, they cause lipid peroxidation and DNA damage. This is where it is important for antioxidants to balance oxidant active molecules. If this balance is disturbed, oxidative stress occurs (Forman et al. 2021).

Antioxidant molecules can be divided into two: enzymes and non-enzymes. Catalase, superoxide dismutase (SOD), glutathione peroxidase and uretensin-II are antioxidant enzymes, while vitamin C, vitamin E, taurine can be given as an example to nonenzymatic molecules. All of these have the properties of cleaning oxidative active molecules and maintaining the oxidant/antioxidant balance (Agarwal et al. 2012).

Oxidative stress plays an important role in many life-threatening diseases (Forrester et al. 2018). Many studies suggest that also oxidative stress plays a role in the pathogenesis of PCOS (Papalou et al. 2016).

In our study, we aimed to investigate the clinical and biochemical findings in PCOS patients; and to determine the levels of antioxidants such as catalase and superoxide dismutase (SOD) and urotensin 2 (UT2), which are oxidative stress markers.

MATERIAL AND METHOD

Prospective randomized study included 75 patients diagnosed with PCOS according to Rotterdam 2003 criteria

and 75 healthy control groups who presented to the Mustafa Kemal University Gynecology and Obstetrics outpatient clinic between September 2016 and February 2017. The demographic data and menstruel cycles of the participants were questioned. The presence of hirsutism was evaluated by using Ferriman-Gallwey score. Morning, fasting blood sampling was performed on the participants. Their lipid profile were measured. Fasting blood glucose and fasting insulin and were measured to identify insulin resistance. hsCRP levels and total testesteron were checked. As antioxydant markers serum catalase, SOD and UT2 levels were determined. The blood samples collected and taken into tubes were centrifuged at 4500 rpm for 10 minutes. Superoxide dismutase, urotensin2 and catalase tests were performed with the cayman kit, sunredbio kit and elabscience kit, respectively, by the micro elisa method. Patients who were under 18 years old, postmenapuasal, who take treatment for hirsutism, pregnancy or lactation that can effect hormon levels, who has thyroid disfunction and patients who use oral contraceptives were excluded from study.

Statistical analysis was done using SPSS 13 package program. Datas were compared by Chi-square for categorical variables, Student-t test for normally distributed variables and Mann-Whitney analysis for non-normally distributed datas. Signifance was defined as p<0,05.

The study was conducted in the Obstetrics and Gynecology Department of Mustafa Kemal University and approved by the Ethics Committee of the Mustafa Kemal University (protocol number 27/10/2016/171). Helsinki Declaration principles were followed in the study. Informed consent forms were obtained from all participants.

RESULTS

150 participants, 75 of whom were PCOS and 75 control groups, were included in the study. The mean age of the PCOS group was 23.1 (±4.9) while the mean age of the control group was 27 (±6.8). Body mass index (BMI) was 23.6 (±4,9) in the PCOS group and 24.1 (±4.9) in the control group. Menstrual disorders are a manifestation of oligo-anovulation. While the duration of menstruation was 47.9 (±26.6) days in the PCOS group, it was 27.5 (±8.2) in the control group (Table 1).

Table 1. Demographic and clinical characteristics of patients

	PCOS (n=75)	CONTROL (n=75)
Age	23,1±4,9*	27±6,8*
Body Mass İndex	23,6±4,9*	24,1±4,9*
Menstruel Cycle	47,9±26,6*	27,5±8,2*
Akantozis Nigricans	12 (%16)	4 (%8)
Hirsutism**	70 (%93)	22 (%30)
PCO ***	67 (%89)	5 (%6)

*mean and standart deviation, **Ferriman-Gallwey score>8, ***policystic ovaries on ultrasound

Laboratory values of the participants in the study are given in the Table 2. Insulin resistance is one of the most common endocrinological disorders in PCOS patients. We took the homa-ir value> 2.5 as the cutoff value for insulin resistance. In our study, while 54% of PCOS patients had insulin resistance, this rate was 21% in the control group. This difference is statistically significant (p<0.05). In PCOS patients total testosterone level was higher compared to the control group, but this difference is not statistically significant (p>0,05). Considering the lipid profile, higher LDL total cholesterol and trigliserid levels are seen in the control group, although it is not significant (p>0.05). Hs-CRP level, an inflammation marker, is higher in the PCOS group.

Table 2. Laboratory Findings of Participants

	PCOS (n=75)	CONTROL (n=75)	p value
İnsulin Resistance*	40 (%54)	15 (%21)	p<0,05
Lh/Fsh>2	11 (%15)	0	p<0,05
Total Testesterone(nmol/l)	0.4±0.2	0.3±0.1	p>0.05
LDL Cholesterol (mg/dl)	94±27	98±31	p>0.05
HDL Cholesterol(mg/dl)	53±13	53±12	p>0.05
Total Cholesterol (mg/dl)	167±32	172±35	p>0.05
Trigliserid (mg/dl)	97±53	100±57	p>0.05
hs-CRP (mg/l)	3.1±2.4	2.1±3.1	p>0.05

*homa-ir>2,5

We used the Ferriman Gallwey system to evaluate hirsutizm. People with a score of> 8 were considered to have hirsutism. PCOS patients had 93% hirsutism, while this rate was only 30% in the control group ($p<0.05$). In our study, total testosterone, one of the laboratory findings of hyperandrogenism, was evaluated. While it was 0.4(±0.2) nmol/l in the PCOS group, it was 0.3(±0.1) nmol/l in the control group. this difference is statistically insignificant ($p>0.05$).

In our study, we looked at SOD, catalase and uretensin-2 levels to evaluate oxidative stress in PCOS. All three antioxidant values were found to be higher in PCOS patients than in the control group (table 3). While this difference was significant in catalase and urotensin-2, it was not statistically significant in SOD.

Table 3. Antioxidant Values

	PCOS (n=75)	CONTROL (n=75)	p value
SOD (U/ml)	1.12±0.55	1.01±0.53	p>0.05
CATALASE (U/ml)	37.4±26.3	28.5±20.7	p<0.05
UROTENSİN-2 (ng/mL)	6.9±4.8	5.1±3.1	p<0.05

SOD:superoksid dismutase; PCOS:policystic ovary syndrome

DISCUSSION

PCOS is a syndrome characterized by the polycystic appearance of the ovaries on ultrasound, anovulation manifested by oligomenorrhea, and clinical and biochemical findings of hyperandrogenism (Norman et al. 2007). In the reproductive age ıt is the most common endocrine disease. Insulin resistance, dyslipidemia, glucose intolerance and obesity are metabolic conditions that may accompany the disease (Toulis et al. 2011). The pathogenesis of polycystic ovary syndrome has not been explained yet and many hypotheses have been proposed. In our study, one of them, oxidative stress, was discussed.

In patients with polycystic ovary syndrome, androgen levels are mostly found to be increased in the circulation. In our study, the total testosterone level was found to be increased, but it was not statistically significant ($p>0.05$). However, when hirsutism was evaluated, hirsutism was found to be 93% in the PCOS group; in other hand it was 30% in control group. We know that free testosterone is more sensitive than total testosterone when we evaluate hirsutizm (Pasquali et al. 2013). When we look up the literature, we see that total testosterone is elevated in women with hirsutism, but remains within normal limits. When evaluating total testosterone, it is recommended to be evaluated together with the decrease in sex hormone binding globuline (SHBG) (Azarchi et al. 2019). SGBG may be effected by factors such as hyperinsulinemy or obesity in our patients. So total testesterone increase was non-significant but significant increase in free testesterone level in our patients could be explained by this concept.

There are studies showing that oxidative stress plays a role in the pathogenesis of PCOS. Mitochondrial mutations also occur in PCOS (Dabravolski et al. 2021).This leads to impaired oxidative phosphorylation, decreased adenosine triphosphate (ATP) production and increased reactive oxygen species (ROS) production. As a result, insulin signaling pathways are disrupted, glucose metabolism is adversely affected and the metabolic and hormonal problems we see in PCOS appear (Zeber-Lubecka et al. 2023). Studies have shown that excessive ROS in the follicular fluid leads to abnormal follicular growth and maturation, resulting in decreased oocyte and embryo quality (Liu et al 2021).

The association of PCOS with oxidative stress has also brought to the agenda the use of antioxidants in its treatment. The glutathione precursor N-acetylcysteine (NAC), a potent antioxidant, has been used to manage PCOS symptoms and has been found beneficial in reducing testosterone levels and increasing FSH levels (Shahveghar et al. 2023).

The potential antioxidant effects of metformin, an insulin sensitizing agent, are thought to be effective in improving PCOS symptoms (Chukwunonso et al. 2016). Inositol is an antioxidant agent that is frequently used in PCOS patients, especially in the treatment of infertility, and provides hormone regulation with a decrease in androgen levels (Monastra et al. 2021).

Various antioxidants have been studied to demonstrate oxidative stress. İn our study we investigated SOD, catalase

and uretensin-2 levels. There are conflicting studies between SOD level and PCOS in the literature. Jeelani had shown increased SOD levels in his study (Jeelani et al. 2019). On the other hand Enechukwu had shown lower level in PCOS (Enechukwu et al. 2019). In our study, we found that increased SOD in PCOS patients compared to the control group, but this increase was not significant. On the contrary, the increase in urotensin and catalase was statistically significant. We can say that we found higher antioxidant levels in PCOS patients in our study. Lifestyle, diet and dietary antioxidant consumption affect antioxidant and oxidant levels. Antioxidant and oxidant status greatly varies between subjects. That could be important factor.

In our study, insulin resistance was found to be significantly higher in PCOS patients. Being overweight is one of the factors affecting insulin resistance. However, when insulin resistance was evaluated in the PCOS patients in our study, we found that being overweight was not a factor. This result may have arisen because insulin resistance is a result of multifactorial factors and our study group was small.

When evaluated in terms of dyslipidemia, the PCOS group had a better lipid profile, although it was statistically insignificant, contrary to expectations. The fact that the PCOS group is younger than the control group can be considered as a possible reason for this. Lipid profile deteriorates with age. The fact that the groups have different mean ages indicates that our samples are not suitable for the evaluation of dyslipidemia.

Our study has some limitations. There is heterogeneity in terms of age between the groups in the study. In addition, the fact that clinical and laboratory findings were not compared with oxidative stress parameters was another limitation of the study. Tests such as SHGB and free testosterone could not be performed.

CONCLUSION

In conclusion PCOS has a highly variable clinical spectrum. Generally, insulin resistance, dyslipidemia, infertility, subfertility and oligomenorrhea are more common in PCOS patients than in normal people. Although its etiology is still not fully elucidated, oxidative stress is thought to play a role. In our study, we found that oxidative stress may have a role in pathogenesis. However, due to inconsistent evidence available in the literature, it is important to elucidate the role of antioxidants such as SOD in PCOS patients.

AUTHOR CONTRIBUTION

Idea/Concept: ŞH, AUH; Design: ŞH, AB; Data Collection and/or Processing: ŞH, AB; Analysis and/or Interpretation: : ŞH, AB, AUH ; Writing the Article: AB, ŞH .

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FINANCIAL DISCLOSURE

This study was supported by Mustafa Kemal University Scientific Research Projects Coordination Unit.

ETHICAL STATEMENT

Permission was obtained from Mustafa Kemal University Clinical Research Ethics Committee for the study (Date of Permission 27/10/2016 file number 171).

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