# Oxidative Stress and Pathogenesis of Polycystic Ovary Syndrome

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**Abstracts:**

**Background:** Polycystic ovary syndrome (PCOS) is considered to be the most common endocrine disorder in reproductive age. It is also one of the most enigmatic diseases. The etiology of PCOS is complex and is uncertain; recently, it has been shown that it is associated with excessive oxidative stress.

**Objective:** Is to find whether PCOS is associated with oxidative stress by measuring one of the oxidative stress markers "malondialdehyde" (MDA).

**Methods:** Between October 20012 and October 2013, fifty PCOS patients and fifty healthy controls were recruited into the study where the following parameters were determined for PCOS patients and compared to healthy control: Serum Follicle stimulating hormone (FSH) and Luteinizing hormone (LH) level along with LH/FSH ratio and testosterone levels. The concentration of MDA as marker of oxidative stress was determined according to Buege & Aust enzymology.

**Results:** The study showed that the body mass index and LH, FSH, LH/FSH ratio, and testosterone were significantly different between the two groups (34.20±2.12 *vs*. 29.23±2.3; P=0.041, 8.83±2.34 *vs*. 8.20±1.76; P=0.012, 4.69±1.62 *vs*. 5.03±1.36; P=0.008, 2.05±0.56 *vs*.1.73±0.39; P=0.001, 2.09±1.27 *vs*. 0.98±1.24; P=0.005 respectively). The serum MDA level is product of lipid peroxidation as the oxidative stress marker where significantly higher in PCOS patients than in healthy controls (0.83±0.56 vs.0.433±0.234; P=0.001).

**Conclusion:** The oxidative stress is increased in PCOS patients indicated by measurement of serum MDA level which is one of the oxidative stress markers and this may contribute to the pathogenesis of PCOS.

**Keywords:** Oxidative stress, polycystic ovary syndrome

## Introduction

Oxidative stress is a general term used to describe the steady state level of oxidative damage to a cell, tissue, organ, caused by the Reactive oxygen species (ROS)[1].ROS are Free radicals derived initially from oxygen which are formed as intermediary products and are a class of powerful oxidants in the human body[2].There is a complex interaction of proxidants and antioxidants that modulates the generation of oxidative stress[1]. Oxidative stress has been suggested to be causative in etiologies such as endometriosis, tubal, peritoneal and unexplained infertility and even polycystic ovary syndrome PCOS [3]. Anovulatory infertility comprises about one quarter of patients attending an infertility clinic. The PCOS is the commonest endocrine disturbance leading to anovulatory infertility and oligomenorrhoea. The morphology of polycystic ovary has been redefined as an ovary with 12 or more follicles measuring 2-9mm in diameter and/or increased ovarian volume (>10cm$^3$)[4].

The decreased antioxidant status and the elevated Oxidative stress levels may contribute to the increased cardiovascular (CV) morbidity in these patients [1].Elevated insulin resistance and hyperhomocysteinemia have been proposed to be caused by Oxidative stress in patients with PCOS [5]. Stimulation of reactive oxygen species (ROS) generation from mononuclear cells (MNCs) by hyperglycemia may play a role in inflammation through the release of TNF-α from circulating MNCs. There is both an increase in oxidative stress and decreased antioxidant status in androgen excess women with PCOS [6].

Aim of this study is to find whether PCOS is associated with oxidative stress by measuring one of the oxidative stress marker "Malondialdehyde" (MDA).

## Patients and Methods:

This case control study included 50 infertile patients with PCOS attending outpatient clinics at Al-Ramadi Maternity Teaching Hospital between October 20012and October 2013. All patients were diagnosed as having PCOS according to the Rotterdam criteria. Patients aged between 18-38 years, no treatment taken during the last 3 months. Exclusion Criteria were history of pelvic surgery, endocrinological disorder in form of hypothyroidism or hyperthyroidism, hyperprolactinemia, and patients with organic uterine or ovarian pathology.

Fifty women matched for age and with regular cycles were selected as control group, they were free of medical illnesses and had not received any medication for >3 months before enrollment.

After taking consent, the following parameters were determined for PCOS patients and healthy control: Serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) level along with LH/FSH ratio, prolactin and testosterone were performed on the third day of normal or progestin induced withdrawal bleeding using Mini-VIDAS system. The serum of the PCOS patients and control also tested for MDA level. The concentration of MDA in serum was determined according to Buege & Aust[7] method enzymology where MDA was formed from breakdown of polyunsaturated fatty acid, served as a convenient index of peroxidation reaction. The thiobarbituric acid (TBA) method was used to measure

the MDA which reacted with TBA to give pink color that was read at (535nm).

Statistical analysis was performed by using Statistical Packages of Social Sciences (SPPS); version 17.0 and also, Microsoft Excel Worksheet 2010. Data are presented as mean±SD of mean. Independent sample t-test used to compare between two groups. The differences between means were considered statistically significant at the level of ($P<0.05$).

**Results:**

The basal clinical and hormonal characteristics of the healthy control and PCOS patients are shown in table1.

Mean body mass index (BMI) was significantly higher in PCOS group than in healthy control (34.20±2.12 *vs*. 29.23±2.3; P=0.041).

Compared with healthy women, women with PCOS presented significantly higher LH (P=0.012), lower FSH (P=0.008), higher LH/FSH ratio (P=0.001) and higher testosterone level (P=0.005).

The serum MDA level is production of lipid peroxidation. The oxidative stress marker (MDA) was significantly higher in PCOS patients than in control (P=0.001) as shown in table 2 and also represented in figure 1.

**Table 1: Characteristics of PCOS patients and control**

| characteristics | PCOS(n=50) | Control(n=50) | P value |
|---|---|---|---|
| **BMI** | 34.20±2.12 | 29.23±2.3* | 0.041 |
| **LH** | 8.83±2.34 | 8.20±1.76* | 0.012 |
| **FSH** | 4.69±1.62 | 5.03±1.36* | 0.008 |
| **LH/FSH** | 2.05±0.56 | 1.73±0.39* | 0.001 |
| **Testosterone** | 2.09±1.27 | 0.98±1.24* | 0.005 |

*significant

**Table 2: MDA level in PCOS patients and control**

| | PCOS (n=50) | Control (n=50) | P value |
|---|---|---|---|
| **MDA** | 0.83±0.56 | 0.433±0.234 | 0.001 |

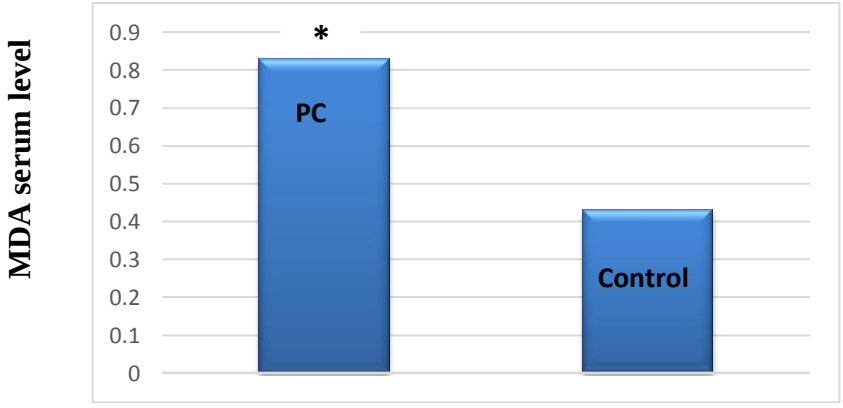


**Figure 1: Serum level of MDA in PCOS and healthy control**

**Discussion**

Malonyldialdehyde is generated as a relatively stable end product from the oxidative degradation of poly-unsaturated fatty acids [8]and it is one of the most frequently used indicators of lipid peroxidation [9,10].Since it is complex measuring free radicals directly in vivo, it is necessary to carry out quantification of cellular components which can react with these free radicals, such as protein, DNA, and many lipids. Once lipid peroxides are unstable compounds, they tend to degrade rapidly in variety of sub products, MDA is one of the most known secondary products of lipid peroxidation, and it can be used as amarker of cell membrane injury [11].

Oxidative stress is an accepted risk factor for the development of CVD [12]. PCOS is also associated with an increase of the risk of CVD. However, the oxidative stress state and the effects of current therapies on this state are not well established in PCOS patients. There are only few studies showing that oxidative stress is increased as in studies of Sabuncu *et. al*. and Fenkçi *et. al.*[6,13].The result of present study agree with the result of Yilmaz *et. al*. who studied the effect of rosiglitazone and metformin on

oxidative stress and homocysteine levels in lean patients with PCOS and found that those women had significantly higher serum MDA levels than healthy women[14].

In the current study a significant increase was reported in level of MDA in PCOS patients compared to healthy control. This goes with the results of the previous three studies and is in agree with that of Al-Omari and Abdul-Qaader [15]who suggested that oxidative stress as part of pathogenesis of PCOS since they found an elevated level of MDA in all their studied PCOS patients.

Alteration in the oxidant-antioxidant profile is known to occur in PCOS [16]. Oxidative stress due to damage brought about by free radicals is also known to influence the response of these patients to therapy [17].Mohan & Priya[17] concluded that oxidative stress is increased in patients with PCOS. They noticed an increase in MDA level along with other oxidative stress markers and suggested that the rise in MDA could be due to the increased generation of ROS due to oxidative damage generated in these patients. Yilidrim *et. al.*[18] reported similar results of elevated MDA level in patient with PCOS. Mehendale[19] found that the levels of MDA, a peroxidative product of essential fatty acids, were increased in infertile women and pointed out to the cause effect relationship between oxidative stress and membrane essential polyunsaturated fatty acids in infertile women.

It has been shown that PCOS is associated with excessive oxidative stress [6].Gonzalez *et. al.* in their study observed that there is generation of ROS from mononuclear cells(MNCs) which occurred in response to hyperglycemia in women with PCOS. This increase in ROS was seen both in obese and lean PCOS when compared to matched controls and was independent of obesity [5]. Disturbed Oxidative stress biomarkers have been observed even in the lean PCOS and significantly lower antioxidant status was measured in the serum of lean PCOS in comparison to healthy controls. Serum MDA, a marker of lipid peroxidation was increased in these subjects [14]. Although this study disagree with the result of Dincer *et. al.*[20],who showed no significant difference in the plasma levels of MDA between women with PCOS and healthy women. The results of the present study seem to agree with of Al-Zobaidi[21]who demonstrated a highly significant elevation in MDA levels and a significant decrease in Glutathione (GSH) values in PCOS patients when compared with those of the control group.

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