REPRODUCTION
SPECIAL REVIEW

OXIDATIVE STRESS AND REPRODUCTIVE FUNCTION

Oxidative stress in polycystic ovary syndrome

Ewa Rudnicka[1], Anna Maria Duszewska[2], Marek Kucharski[1], Paweł Tyczyński[3] and Roman Smolarczyk[1]

[1]*Department of Gynaecological Endocrinology, Medical University of Warsaw, Warsaw, Poland,* [2]*Department of Morphological Sciences, Faculty of Veterinary Medicine, Warsaw, University of Life Science, Warsaw, Poland and* [3]*Department of Interventional Cardiology and Angiology, National Institute of Cardiology, Warsaw, Poland*

Correspondence should be addressed to E Rudnicka; Email: ewa.rudnicka@poczta.onet.pl

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Abstract

In brief: A genetic, epigenetic, and environmental association exists between oxidative stress (OS) and polycystic ovary syndrome (PCOS), expressed in a multifaceted clinical profile. This review summarizes and discusses the role of OS in the pathogenesis of PCOS syndrome, focusing on metabolic, reproductive, and cancer complications.

Abstract: Oxidative stress (OS), an imbalance between oxidants and antioxidants in cells, is one of many factors playing essential roles in the pathogenesis of polycystic ovary syndrome (PCOS). PCOS is described mainly as a disproportion of reproductive hormones, leading to chronic anovulation and infertility in women. Interestingly, OS in PCOS may be associated with many disorders and diseases. This review focuses on characteristic markers of OS in PCOS and the relationship between OS and PCOS related to insulin resistance (IR), hyperandrogenemia, obesity, chronic inflammation, cardiovascular diseases, and cancer. Interestingly, in patients with PCOS, an increase in oxidative status and insufficient compensation of the increase in antioxidant status before any cardiovascular complications are observed. Moreover, free radicals promote carcinogenesis in PCOS patients. However, despite these data, it has not been established whether oxygen stress influences PCOS development or a secondary disorder resulting from hyperglycemia, IR, and cardiovascular and cancer complications in women.

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, with a 5–10% prevalence rate in reproductive-aged women. It is characterized by (1) chronic anovulation, (2) biochemical and/or clinical hyperandrogenism, and (3) polycystic ovarian morphology (Escobar-Morreale 2018, Rudnicka *et al.* 2021a,b). Diagnosis of this syndrome is based on the Rotterdam criteria in 2003 when two out of three characters were found, while other etiology has been excluded (ESHRE/ASRM 2004).

PCOS has significant clinical implications and can lead to health problems related to insulin resistance (IR), hyperandrogenemia, chronic inflammation, cardiovascular diseases (CVDs), obesity, and cancers and is the leading cause of chronic anovulation and infertility (Vilmann *et al.* 2012, Murri *et al.* 2013, Desai *et al.* 2014, Carvalho *et al.* 2018, Herman *et al.* 2019, Shaaban *et al.* 2019, Karimi *et al.* 2020, Duică *et al.* 2021, Rudnicka *et al.* 2021a,b). It is worth emphasizing that similar features of PCOS can be observed in some animals (Ryu 2019). Interestingly, biochemical markers of PCOS also may occur in males whose female relatives are afflicted with PCOS because of the inheritance of specific susceptible genes responsible for PCOS. It is possible because the genetic risk factors for PCOS can act independently of ovarian function, causing hormonal, metabolic, and clinical symptoms through biological pathways common to men and women (Di Guardo *et al.* 2020).

The reasons for the development of PCOS have not been fully understood, which may indicate that the etiology of this disorder is three-dimensional (multifactorial, multi-pathway, and multilevel), which would explain the heterogeneity of this disease. Moreover, some studies suggest that PCOS may be a complex multigene disorder with solid epigenetic and environmental influences (Escobar-Morreale 2018, Bruni *et al.* 2022, Mancini *et al.* 2021).

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One of the debated causes of PCOS is oxidative stress (OS) (Murri *et al*. 2013, Desai *et al*. 2014). However, it has not been established whether oxygen stress affects the development of PCOS or whether it is only a secondary disorder resulting from hyperglycemia and IR occurring in women. This review aims to summarize and discuss previous and recent findings concerning the relationship between OS and PCOS.

Oxidative stress

OS is a physiological imbalance between oxidants and antioxidants in the body. Oxidants (free radicals), which are unstable and highly reactive, acquire stability by stealing electrons from other molecules, which are antioxidants. Otherwise, the free radicals lead to cellular damage and even death. Therefore, both increased levels of oxidants (free radicals or reactive species) and a decrease in antioxidant defense mechanisms may cause OS (Agarwal *et al*. 2012, Murri *et al*. 2013, Rahal *et al*. 2014, Kurutas 2016, Zuo *et al*. 2016, Pizzino *et al*. 2017, Ighodaro & Akinloye 2018, Mohammadi 2019).

Oxidants

There are two main classes of free radicals or oxidants: reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Agarwal *et al*. 2012, Rahal *et al*. 2014, Pizzino *et al*. 2017, Ighodaro & Akinloye 2018). However, other oxidants include advanced glycation end products (AGEs). Interestingly, AGEs promote the creation of ROS and RNS through multiple mechanisms (Chen *et al*. 2018, Tatone *et al*. 2021).

Physiologically, oxidants regulate several cellular processes, including proliferation, differentiation, development, migration, cytoskeletal dynamics, and metabolism. In pathological states, oxidants are available in excess. They react with lipids, proteins, and nucleic acids, thereby altering target molecules' structural and functional properties. OS damages cellular structures, especially DNA and mitochondria, and can lead to extensive cell, tissue, and organ dysfunction and damage (Agarwal *et al*. 2012, Rahal *et al*. 2014, Pizzino *et al*. 2017, Ighodaro & Akinloye 2018).

The long-term effects of OS include degenerative diseases, a decrease in the body's immunity and an increased risk of developing many dangerous diseases, such as atherosclerosis and CVDs that may lead to a stroke or heart attack. Another group of diseases that scientists believe are associated with OS are neurodegenerative diseases such as Alzheimer's and Parkinson's. In addition, OS may promote the development of neoplasms, mainly melanoma. OS is also crucial in developing diseases of the lungs, stomach, kidneys, and urinary system (Agarwal *et al*. 2012, Rahal *et al*. 2014, Pizzino *et al*. 2017, Ighodaro & Akinloye 2018).

Antioxidants

Based on the biochemical classification, antioxidants include two main categories: enzymatic and non-enzymatic. Enzymatic antioxidants are natural, key enzymes that can detoxify excess ROS and RNS, including superoxide dismutase (SOD), catalase, and glutathione peroxidase. In contrast, non-enzymatic antioxidants are exogenous and endogenous molecules such as glutathione, thioredoxin, vitamin C, vitamin A, vitamin E, selenium, and zinc (Zn) (Pizzino *et al*. 2017, Ighodaro & Akinloye 2018).

The effect of OS, nitrosation stress, and glycation can be assessed by measuring the level of specific oxidants and antioxidants or the mutual influence between different types of oxidants and antioxidants.

Oxidative stress in PCOS

OS can be considered in many aspects, but one of the most interesting is the relationship between OS in PCOS. Many researchers revealed that OS level is significantly increased in patients with PCOS and obesity, IR, cardiovascular disorder, and cancers (Gonzalez *et al*. 2012a, Lim *et al*. 2012, Papalou *et al*. 2016, Vilmann *et al*. 2012, Blair *et al*. 2013, Desai *et al*. 2014, Zuo *et al*. 2016, Fatima *et al*. 2019, Sandhu *et al*. 2021, Cheng & He 2022).

Interestingly, these disorders can be observed either separately or with different disease units and in combination with each other, complicating diagnosis and treatment.

The pathogenesis of PCOS in the context of OS may involve disorders of cellular organelles and molecular and biochemical processes. The most relevant example may be the relationship between mitochondrial dysfunction and PCOS, in which OS may also be involved (Zhang *et al*. 2019, Shukla & Mukherjee 2020, Malamouli 2022). It has been suggested that decreased mitochondrial O_2 consumption, glutathione, and increased ROS contribute to mitochondrial dysfunction in PCOS patients (Shukla & Mukherjee 2020).

The effect of OS, nitrosation stress, and glycation can be assessed by measuring the level of specific oxidants and antioxidants or the mutual influence between different oxidants and antioxidants. Oxidant and antioxidant markers provide insights into developing and treating OS-related disorders (Enechukwu *et al*. 2019, Fatima *et al*. 2019). OS markers can usually be detected in serum and follicular fluid (Liu *et al*. 2021). Interestingly, these markers are used to provide insights into the development and treatment of OS-related disorders (Forman & Zhang 2021). The essential diagnostic PCOS markers in the clinical aspects are shown in Fig. 1.

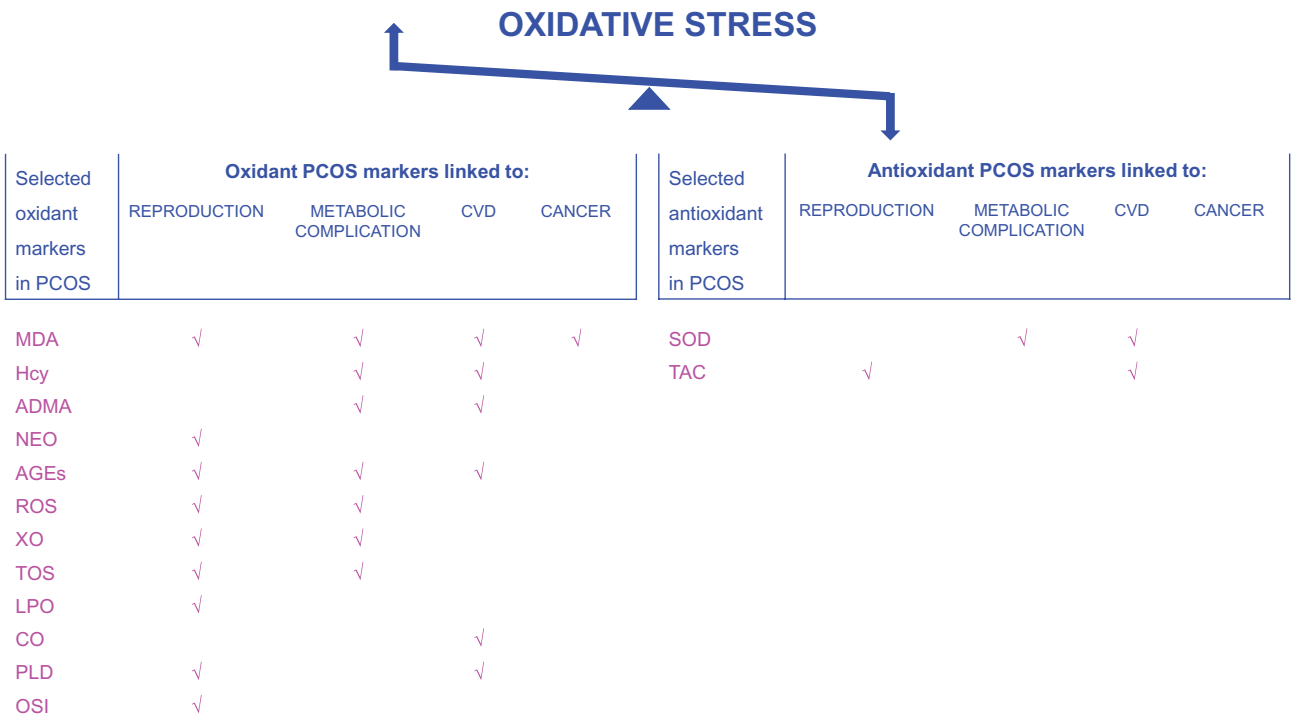

Figure 1 The selected markers of oxidative stress (oxidants and antioxidants) in polycystic ovary syndrome (PCOS) linked to reproduction, metabolic complication, cardiovascular disease (CVD), and cancer. Oxidants: ADMA, asymmetric dimethylarginine; AGEs, advanced glycosylated end products; CO, protein carbonyl; Hcy, homocysteine; LPO, lipid peroxidation; MDA, malondialdehyde; NEO, neopterin; OSI, oxidative stress index; PLD, prolidase; ROS, reactive oxygen species; TOS, total oxidant status; XO, xanthine oxidase. Antioxidants: SOD, superoxide dismutase; TAC, total antioxidant capacity.

Characteristics of the most representative markers of oxidative stress in PCOS

Oxidant markers in PCOS

Malondialdehyde (MDA) is a highly reactive compound that occurs as an enol and is one of the final products of polyunsaturated fatty acids (PUFAs) peroxidation in the cells. An increase in free radicals causes the overproduction of MDA. Its level is a marker of OS and antioxidant status in cancerous patients. Interestingly, the level of MDA increases both in PCOS and obesity but also in hyperandrogenism and IR (Uçkan *et al.* 2022).

Homocysteine (Hcy) is a sulfuric amino acid formed by the demethylation of the methionine amino acid. The mean serum Hcy concentrations are increased in women with PCOS, but the mechanism by which Hcy is increased in PCOS patients is not well-read. Among the risk factors, it was described that the Hcy level is highly linked to obesity and IR in PCOS patients. However, Hcy increases CVD risk in PCOS patients (Maleedhu *et al.* 2014, Maharjan & Hong 2018, Herman *et al.* 2019, Wu *et al.* 2021).

Asymmetric dimethylarginine (ADMA) is an endogenous competitive nitric oxide (NO) synthase inhibitor. There is a strong association between PCOS and obesity, IR, CVD, and diabetes. In addition, ADMA is seen as a marker for endothelial dysfunction (ED) and cardiovascular morbidity. A higher level of ADMA can indicate additional mechanisms of cardiovascular risks in PCOS patients other than IR (Toulis *et al.* 2011, Yavuz *et al.* 2014).

Neopterin (NEO) is an oxidized form of 7,8-dihydroneopterin. NEO is a diagnostic biomarker of infection and illness. NEO concentrations in body fluids can indirectly estimate the degree of OS emerging during the cell-mediated immune response. Moreover, recently NEO was found to be capable of enhancing toxic effects induced by ROS. NEO is altered in women with PCOS, independent of BMI (Alanbay *et al.* 2012, Gieseg *et al.* 2018).

AGEs are a heterogeneous class of molecules mainly formed by a multistage chemical transformation named the Maillard reaction. AGEs include 20 compounds derived from macromolecules from endogenous non-enzymatic glycation and absorbed exogenous sources. AGEs include pyrraline, Nε-carboxy-methyl lysine, Nε-carboxy-ethyl lysine, pentosidine, argpyrimidine, derivatives of methylglyoxal (MG), hydroimidazolones derived from MG, glyoxal, 3-deoxyglucosone (3-DG), arginine-derived Nδ-ornithine and bis (lysyl) imidazolium derivatives, such as methylglyoxal-lysine dimer (MOLD) and glyoxal-lysine-dimer (GOLD) (Chen *et al.* 2018, Tatone *et al.* 2021). The increase in the AGE level is a common feature in all PCOS phenotypes.

AGEs activate signaling pathways, leading to increased OS, inflammation, hyperandrogenism, IR, and ovulatory dysfunction. AGEs are important risk factors for CVD in PCOS women (Diamanti-Kandarakis *et al.* 2007, Tatone *et al.* 2021).

ROS derive from molecular oxygen, formed upon the incomplete reaction of oxygen. ROS include: superoxide anion (O_2^-), hydroxyl radical (OH^-), singlet oxygen, hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), hydroxyl radical (OH), hydrogen peroxide (H_2O_2), organic hydroperoxide (ROOH), alkoxy and peroxy radicals (RO and ROO), hypochlorous acid (HOCl), and peroxynitrite (ONOO). Increased levels of ROS are observed in PCOS women with hyperglycemia, independent of the presence of obesity and abdominal adiposity. Moreover, women with PCOS displayed the highest levels of ROS with poorer fertilization rates (Karuputhula *et al.* 2013, Diamanti-Kandarakis *et al.* 2017).

Xanthine oxidase (XO) is an enzyme that catalyzes the oxidation of hypoxanthine to xanthine and accelerates the oxidation of xanthine to uric acid. Therefore, XO levels increase in PCOS patients and are a valuable marker for assessing OS. Also, positive correlations between XO and inflammatory markers and risk factors for CVD suggest that XO plays a significant role in the pathogenesis of PCOS and its metabolic complications (Isik *et al.* 2016).

Total oxidant status (TOS) is a marker of the overall oxidation state of the body. The increased level of TOS in women with PCOS is significantly higher in serum and follicular fluid. Interestingly, a decrease was determined in TOS levels after both oral glucose tolerance and mixed meal tests in the PCOS patients (Kucukaydın *et al.* 2016, Mazloomi *et al.* 2021).

Lipid peroxidation (LPO) is a process under which oxidants such as free radicals attack lipids containing carbon–carbon double bond(s), especially PUFAs. LPO products include MDA and hydroxyl radicals, which accumulate due to intracellular and cell wall damage involving PUFAs, with increased levels of ROS serum. Changes in LPO processes in patients with PCOS were compensatory, manifested in increased α-tocopherol and retinol concentrations and a moderate decrease in SOD activity (Ayala *et al.* 2014, Kolesnikova *et al.* 2017, Enechukwu *et al.* 2019).

Protein carbonyl (CO) or protein carbonylation refers to a process that forms reactive ketones or aldehydes that can be reacted by 2,4-dinitrophenylhydrazine to form hydrazones. CO levels are significantly higher in women with PCOS than in healthy women. Moreover, high-density lipoprotein levels are inversely associated with CO levels (Cheng & He 2022).

Prolidase (PLD) is a ubiquitously expressed cytosolic metalloproteinase, the only enzyme capable of cleaving imidodipeptides containing C-terminal proline or hydroxyproline. The significant difference between PLD levels in PCOS and control shows that it may be used as a diagnostic marker for the disease. In addition, there is a positive correlation between PLD levels and the number of cysts, and hence may be used as a prognostic marker to monitor disease status (Bhatnager *et al.* 2018, Eni-Aganga *et al.* 2021).

OS index (OSI) is the ratio of the TOS to total antioxidant status (TAS) and is considered a more precise biomarker reflecting OS. OSI can reflect the imbalance between oxidants and antioxidants through comprehensive measurement of TAS and TOS. The characteristic is that PCOS women show higher basal serum TOS and OSI levels than healthy ones (Gong *et al.* 2020, Cheng & He 2022).

Antioxidant markers in PCOS

SOD is a metalloenzyme and hence requires a metal cofactor for its activity as iron (Fe-SOD), zinc (Zn-SOD), copper (Cu-SOD), and manganese (Mn-SOD). SOD is the first detoxification enzyme and the most potent antioxidant in the cell. SOD is considered an essential antioxidant. Although recent studies have shown that SOD levels in PCOS fluctuate from study to study (Abudawood *et al.* 2021, Talat *et al.* 2022).

Total antioxidant capacity (TAC) is the group of non-enzymatic antioxidants and indicates antioxidants' ability to counteract OS-induced damage in cells. Significantly lower levels of serum TAC were observed in PCOS patients, which may suggest increased OS in such patients. However, when the serum level of TAC is significantly lower, the level of TOS is considerably higher (Kanafchian *et al.* 2020).

Oxidative stress and its role in the pathogenesis of PCOS-related disorders

Oxidative stress and reproduction in women with PCOS

Oxidative metabolism is also an essential intraovarian regulator of folliculogenesis. Each month, a cohort of follicles begins to grow and develop in the ovary, but only one develops into the dominant follicle (Agarwal *et al.* 2012). This process is controlled by an increase in ROS and inhibited by antioxidants, while antioxidants support the progression of meiosis II. ROS affects meiosis II progression, diminishes gonadotropin secretion and DNA damage, and inhibits ATP production (Behrman *et al.* 2001). Free radicals and antioxidants play a crucial role in the ovarian environment during the oocyte maturation and luteal phases (Sugino *et al.* 2006). PCOS is associated with decreased antioxidant concentration. It is one of the states with increased OS, leading to disturbance in the cycle of ovarian follicular and luteal phases (Agarwal *et al.* 2012). Follicular fluid in women with PCOS demonstrated increased levels of ROS and

MDA. It decreased TAC, which was directly associated with reduced oocyte maturation and fertilization rates, poor embryo quality, and lower pregnancy rates (Das *et al*. 2006, Singh *et al*. 2013, Nuñez-Calonge *et al*. 2016). Also, AGEs affect the ovarian cells directly in women with PCOS. It was investigated that PCO ovaries displayed an increased concentration of AGE deposition in granulosa, theca, and ovarian endothelial cells (Mehri *et al*. 2014). Diamanti-Kandarakis *et al*. found higher expression of RAGE and NF-kB p65 in granulosa cells (Diamanti-Kandarakis *et al*. 2007).

There are many studies concerning the putative role of OS infertility (Das *et al*. 2006, Singh *et al*. 2013, Nuñez-Calonge *et al*. 2016). A large part of them involve women undergoing assisted reproductive techniques. Significantly, increased MDA, ROS, NO, and LPO levels in follicular fluid have been found in women with failures during artificial reproductive techniques (ART) (Das *et al*. 2006, Nuñez-Calonge *et al*. 2016). In contrast, follicular fluid TAC was positively associated with success rates, in which plasma antioxidant status was shown to be beneficial in achieving pregnancy in those groups of patients (Bedaiwy *et al*. 2012, Velthut *et al*. 2013).

Oxidative stress and metabolic complications in PCOS

PCOS and its metabolic complications may be caused by abdominal obesity, which is conducive to developing IR and compensatory hyperinsulinemia (Escobar-Morreale *et al*. 2018). Regarding pathogenesis of IR in PCOS women, it has been investigated that with the increased OS, various protein kinases are activated, leading to serine/threonine phosphorylation of insulin receptor substrate (IRS), inhibit normal tyrosine phosphorylation of IRS, and finally are the cause of degradation of IRS and IR (Diamanti-Kandarakis & Dunaif 2012, Pollak *et al*. 2012).

Hyperglycemia, which is the consequence of hyperinsulinemia, has been thought to play a role in inflammation through the production of TNF-α, a known mediator of IR secreted by mononuclear cells (MNCs) (Costello *et al*. 2007, Gonzalez *et al*. 2012a,b). The MNCs produce ROS, resulting in cellular damage, activating nuclear factor-κB, which promotes the transcription of TNF-α. In this way, OS creates an inflammatory environment that further increases IR and contributes to hyperandrogenism (Gonzalez *et al*. 2006, Agarwal *et al*. 2012).

OS markers are of great importance in explaining the mechanisms between OS, hyperinsulinemia, and PCOS.

In the study by Uckan *et al*., the mean serum MDA level was statistically significantly higher in the obese PCOS group compared to the nonobese PCOS and the control group. There was also a statistically significant difference between nonobese PCOS and the control group in MDA serum concentration. A positive correlation between MDA and HOMA-IR, insulin and BMI in the PCOS patients group was observed in the cited research. The authors concluded that the PCOS symptoms are associated with metabolic syndromes, such as hyperinsulinemia, obesity, and dyslipidemia, which were exacerbated by increased OS (Uçkan *et al*. 2022, Zhao *et al*. 2016). Chen *et al*. investigated the association between abdominal obesity, IR, and OS in adipose tissue in women with PCOS (Chen *et al*. 2014). They found that PCOS was associated with lower expression of glucose transporter 4 and IRS1 in visceral adipose tissue (VAT), which was strongly correlated with waist circumference and HOMA-IR. They also observed that PCOS is associated with increased OS in VAT. The expression of the protein oxidative damage product 3-nitrotyrosine residues (nitrotyrosine) was stronger in PCOS women. This study also demonstrated that oxidative protein damage was more evident in perivascular regions than in other parts, indicating that endothelium oxidation stress plays a crucial role in the IR in VAT in PCOS and may be a primary process leading to IR.

Concerning metabolic dysfunction, it is also well established that AGEs, which are elevated in women with PCOS, are closely linked to IR. The study by Cai *et al*. found that mice fed with a high-AGE diet showed abdominal adiposity, IR, and even diabetes compared with mice fed with an isocaloric AGE-free diet (Cai *et al*. 2012). Tantalaki *et al*. found that lower dietary AGE intake in women with PCOS decreased serum AGE, HOMA-IR and OS markers (Tantalaki *et al*. 2014).

Another study found that reducing OS by improving antioxidant defenses through body fat mass reduction, pharmacological agents, exercise, and/or dietary modification may have beneficial effects in women suffering from PCOS (Chen *et al*. 2018, Cheng & He 2022).

Another disorder associated with PCOS and IR is the nonalcoholic fatty liver disease (NAFLD) (Watt *et al*. 2019), one of the common causes of chronic liver disease in the Western world with a prevalence of 6.3–33% in the general population (Chalasani *et al*. 2012). It is defined as >5% fat accumulation in the liver without secondary causes, such as viral hepatitis, excessive alcohol consumption, drug-related liver disease, autoimmune liver disease, genetic metabolic liver disease, and other diseases (Perumpail *et al*. 2017). NAFLD includes not just benign forms such as hepatic steatosis (fat accumulation in liver tissue without inflammation) but also steatohepatitis (fat accumulation in liver tissue with inflammation and hepatocellular injury) with or without fibrosis, which could be the reason for liver cirrhosis and possibly hepatocellular carcinoma (Jarvis *et al*. 2020). Similar to PCOS, NAFLD is strongly associated with obesity, IR, cardiovascular disorders, and type 2 diabetes mellitus. The main risk factors for NAFLD in PCOS include hyperandrogenemia, IR, obesity, chronic

low-grade inflammation, and OS (Wang & He 2022). Inflammation is linked to the pathogenesis of PCOS, and low-grade inflammation mediates IR in PCOS patients. IR leads to hyperinsulinemia which, on the other hand, is responsible for a decrease in mitochondrial fatty acid oxidation, generation of inflammation, necrosis, and fibrosis that finally leads to the progression of NAFLD (Engin 2017).

Oxidative stress and risk of cardiovascular disease in PCOS

The variety of CVDs has heterogeneous pathophysiologic mechanisms, where OS has been confirmed as one of the potential causes. OS is an accepted risk factor in the pathogenesis of atherosclerotic plaques, subsequent coronary artery disease (CAD) and acute coronary syndromes (ACS). Concerning the mechanism by which OS affects cardiac function at the cellular level, it has been found that the incidence of hypertension may be due to vasoconstriction resulting from a decreased availability of NO due to increased ROS levels (Duică *et al.* 2021). The increase in ROS levels impacts cardiac function by negatively influencing calcium signals leading to arrhythmia. It could also influence cardiac remodeling and atherosclerotic plaque formation (Godo & Shimokowa 2017, Senoner & Dichtl 2019, Zhang *et al.* 2020, Hyderali & Mala 2021).

OS is also one of the mechanisms that trigger ED, which is a signature event in the development of atherosclerosis (Silva *et al.* 2012). Endothelin-1 (ET-1), which induces OS, is known as one of the best-studied markers of ED and abnormal vascular reactivity (Yanagisawa & Masaki 1989) and is elevated in some insulin-resistant states, such as obesity, atherosclerosis, and also in PCOS (Diamanti-Kandarakis *et al.* 2001). Insulin stimulates ET-1, leading to an increase in OS and the development of atherosclerotic lesions in hyperinsulinemic conditions like PCOS.

However, redox processes are characterized by heterogeneous nature. The association of different biomarkers related to OS with stable angina and ACS is not uniform. Many OS-related biomarkers belonging to different pathways have been previously evaluated. New biomarkers like lectin-like oxidized low-density lipoprotein receptor-1 are recently emerging. Some studies show that patients presenting with ACS may have a more deteriorated antioxidant status than stable CAD patients and healthy controls (Lubrano *et al.* 2019). A small study indicated an increase in oxidant status and insufficient compensatory increase of antioxidant status in PCOS patients before any cardiovascular complications occurred. A studied group of 27 PCOS patients without CVD or traditional CVD risk factors were matched to 18 controls. PCOS patients revealed significantly higher levels of MDA (one of the end-products of LPO) (Sabuncu *et al.* 2001). These data were confirmed by observations from another study, which also showed increased oxidant stress (measured by CO content) and decreased antioxidant levels (measured by TAC) in PCOS (Fenkci *et al.* 2003).

In conclusion, the levels of vasoconstrictors, biomarkers of OS and CVD are significantly higher in PCOS patients than in control groups. Furthermore, the elevated level of those risk factors is strongly correlated with a higher prevalence of atherosclerotic plaques, subsequent CAD, and ACS.

Oxidative stress and cancer risk in PCOS patients

It has been proven that OS may be related to cancer pathogenesis (Federico *et al.* 2007). Free radicals promote carcinogenesis through DNA damage and epigenetic changes (Zuo *et al.* 2016). Based on many meta-analyses, the risk of endometrial cancer among PCOS patients is a 2.7-fold increase compared to healthy women (Chittenden *et al.* 2009). However, a major British study of 30 years of observation follow-up showed no differences in the incidence of ovarian cancer between women with PCOS and the healthy women group (Pierpoint *et al.* 1998). However, another large case-control study showed a 2.5-fold increased risk among PCOS women (Schildkraut *et al.* 1996).

Several pathomechanisms could be responsible for these results. Anovulatory cycles in PCOS women result in the effects of estrogens that are not compensated by progesterone. This leads to excessive endometrial proliferation, which can cause endometrial hyperplasia. Due to OS, estradiol metabolites are not methylated and cannot be eliminated. This can induce a change in the nucleotide sequence, resulting in DNA mutations and initiating carcinogenesis (Zuo *et al.* 2016).

OS is also one of the factors responsible for IR, which often coexists with PCOS. Those reactive species disrupt insulin cell signaling pathways, worsening sensitivity for this hormone (Evans *et al.* 2005). In addition, because insulin receptors exist in the endometrium, elevated insulin levels have a mitogenic effect on endometrial cells, which may cause the development of endometrial cancer (Giudice LC 2016). Moreover, elevated glycemia and free fatty acids in this group of patients cause excessive production of free radicals, which might exacerbate IR (Zuo *et al.* 2016).

As PCOS is commonly associated with obesity, which is a well-proven risk factor for endometrial cancer, it cannot be excluded that a higher BMI might interfere with the presented results (Dumesic & Lobo 2013). Chronic systemic inflammation and elevated ROS, common in obese patients, are widely considered to be the underlying factors of pathophysiology carcinogenesis in this group of people (Nasiri *et al.* 2015). Furthermore, many studies show that obesity is a risk factor for endometrial cancer and all gastrointestinal cancers,

including pancreas, liver, ovary, breast, and kidney (Calle *et al.* 2003).

Hyperandrogenemia is one of the three Rotterdam diagnostic criteria of PCOS (Tedee *et al.* 2018). In addition, animal model studies performed on rats with dihydrotestosterone-induced PCOS reveal that hyperandrogenemia can exacerbate IR, cause dyslipidemia, and is linked with elevated OS markers like glutathione or SOD (Tepavčević *et al.* 2015). This, in an indirect way, might play a role in carcinogenesis, but the data are scanty, and the significance of elevated androgens needs further research, as some studies suggest their protective role on human cells against inflammation (Gonzalez *et al.* 2012a).

Conclusions

PCOS is one of the most common endocrine disorders in women of reproductive age, presenting heterogeneous clinical manifestations with different phenotypes. Despite a long history of studies on PCOS, its etiology is still unknown. However, recent research suggests that PCOS may be a complex multigene disorder with solid epigenetic and environmental influences. Numerous studies have shown more significant levels of OS markers in PCOS patients. OS, as the imbalance between oxidants and antioxidants in PCOS patients, may contribute to the risk of metabolic syndrome, IR, hyperandrogenemia, CVDs, reproductive failure, and an increase in cancer risk. Moreover, oxidant and antioxidant status varied between individuals, considering differences in diet, BMI, and enzymatic and dietary antioxidants. Thus, further studies are needed to standardize each biomarker's measurement and understand the pathophysiology of OS and its effect on PCOS.

Review criteria

A search for original articles published between 1996 and 2022 focusing on OS in PCOS was performed in PubMed, Web of Science, and Scopus. The search terms used were oxidative stress, oxidative marker, polycystic ovary syndrome, oxygen species in PCOS, oxidative stress in insulin resistance (IR), hyperandrogenemia, obesity, cardiovascular diseases (CVD), and necrosis. The resulting references, including reviews, were used as leads for further literature searches.

Declaration of interest

The authors declare no conflict of interest.

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Author contributions statement

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