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Oxidative Stress and Its Role in Insulin Resistance in Polycystic Ovary Syndrome

Farideh Zafari Zangeneh[1]

1. Associate Professor of the Reproductive Health Research Center, Tehran University of Medical,Tehran,Iran

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ABSTRACT

The production of reactive oxygen species (ROS) can alter macromolecules in living organisms and can result in a wide range of injuries. Recently, oxidative stress has been known as a key mechanism in insulin resistance. Today, oxidative stress (OS) status assessment is performed using circulating markers such as malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GPX). Polycystic ovary syndrome (PCOS) with a prevalence of 4-12 % is the most common endocrine-metabolic disorder in the reproductive age of women. PCOS is now recognized as an important metabolic disorder. Insulin resistance (IR) independent of obesity in PCO women has been identified as a predisposing factor for type2 diabetes and cardiovascular disease (CVD). Oxidative stress index is strongly associated with PCOS. The role of oxidative stress is very important but not considered but it plays an important role in the development of IR. In this mini review, we presented a viewpoint about the key role of brain's IR/OS in the brain-ovarian axis in the women with PCOS. These review articles helps us to better understanding of the PCO etiology

1. Introduction

1. Polycystic ovary syndrome (PCOS)

This syndrome is associated with endocrine/metabolic disorders and infertility. Its prevalence is 4-12% in women of reproductive age (1). In Iran, the prevalence of this syndrome has been reported from 7.1 to 14.6 (2). PCOS is heterogeneous in clinical signs and the anovulation in these women is the main cause of infertility. The anovulation accounts approximately 75% of infertility in these women (3). In the childhood, early puberty, in adolescence hirsutism, menstrual disorder and, after post-adolescence with infertility and glucose intolerance and finally in middle age is associated with diabetes mellitus, cardiac vascular disordes (CVD) and blood pressure (BP). PCOS etiology is still unknown. The cause of this syndrome can be the complex pathology with endocrine/metabolic dysfunction in the two brain axes: hypothalamus-pituitary-adrenal (HPA) and gonadal (HPG). The metabolic pathways in ovary like: steroids and gonadotropin regulators, glucose metabolism regulators, adipose signaling and important insulin signaling pathways that all of them are destroyed in this syndrome (4). Polycystic ovary mophology (PCOM) is one of the most valuable clinical finding in this chronic syndrome. These morphological changes were first described by Chereau in 1844 (5). Diagnostic criteria for this syndrome have been established by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproduction and Infertility (ASRM) in 2003, based on extensive studies over the past several decades with the so-called Rotterdam criteria (6). Some researchers doubt whether this syndrome is an evolutionary paradox or a sexual conflict, which may be related to heredity, environmental factors and even intra-fetal factor or factors (7). As a syndrome, PCOS is also treated on the basis of precise clinical symptoms, and therapies mainly include ovulation induction, lowering the levels of androgen, luteinizing hormone (LH), insulin resistance, and surgery (8). The assisted reproductive technologies (ART) method is another method (in vitro oocyte maturation) for infertile patients with PCO.

2. Oxidative Stress (OS)

Oxidative stress is an important factor for the instability at intracellular homeostasis. Any factor or many conditions can lead to the production of reactive oxygen species (ROS) which is called oxidative stress. In the normal cells, there must be a relative balance between prooxidants and antioxidants for internal stability. Disruption of this balance can lead to oxidative stress by increasing prooxidants or decreasing antioxidants, so that prolonged these imbalance can easily cause serious injury for normal cells (9).

2.1. Oxidants

Oxidation is a chemical process for destroying the electrons of an atom or molecule that can be critical (10). Oxidants are chemical compounds that produce molecular oxygen (prooxidants) that must be neutralized by antioxidants. The cell can tolerate oxidative stress to a limited extent, but in severe status, damaged cell membrane may cause a pathological complications with the impaired of cell homeostasis (11).

Todays, antioxidants are used as chemical prophylaxis for inhibiting of the free radicals (12).

2.2. Free radicals

Free radicals can easily enter in the chemical reaction via sharing of their single electrons. Oxygen free radicals are the most invasive agents in the biological systems that can damage the chain pathways. These agents are generally known as "reactive oxygen species" (ROS). ROS contains free and non-free radical oxygen molecules that are involved in the generation of oxidative stress (13). Oxidative stress by overproducing reactive oxygen species and accumulating them during environmental stress can even damage the crop and reduce the quality and quantity of the crop, even in plant products. The production of reactive oxygen species as a determining factor can cause lipid peroxidation, inactivation of enzymes and oxidative damage of cellular DNA. The main site of free radical production is mitochondry (14).

2.3. Mitochondria and oxidative stress

The critical role of mitochondria in cell energy homeostasis is crucial, so they are involved in biogenetic processes including: insulin signaling, cell survival control, and also the major site of ROS production in the cell during respiratory reactions for their intracellular respiratory chain. Thus, abnormalities in the mitochondria function can be highly linked to the progress of peripheral IR (15, 16). Mitochondrial-ROS (mtROS) producing plays an important role in the release of pro-apoptotic proteins such as cytochrome-c to produce of caspase initiation and apoptosis. Therefore, there is evidence for the direct relationship between mitochondria, oxidative stress, and cell death (17). In addition, mitochondria-ROS producing during cellular metabolism can be generated in response to various environmental stimuli including: growth factors, inflammatory cytokines, ionizing radiation, UV, chemical oxidants, chemotherapy, hyperoxia, toxins and metals (18). Apart from the traditional role of mitochondria in metabolic processes and ROS signaling it has been dynamically implicated ininnate immunity (19). "Recently, it has become clear that some innate immune cells are epigenetically reprogrammed or “imprinted” by past experiences. These “trained” innate immune cells display altered inflammatory responses upon subsequent pathogen encounter" (20). The reactive oxygen species in mithochondria (mtROS) as the signaling molecules can drive production of the inflammatory cytokine and T cell activation. Increasing of mtROS level can lead to autoimmune diseases, CVD, cancers (21). Findings from recent decades show that dysfunction of the endothelial cell by inflammatory and oxidative stress can be associated with the pathogenesis of diabetes for development of premature atherosclerosis. Therefore, antioxidants can be effective role in suppressing of the inflammatory cytokines secration in the human coronary artery endothelial cells (22).

2.4. Antioxidants

Antioxidants must be control the autoxidation by disconnecting the transmission of free radicals or by preventing of the formation of free radicals for reduction of oxidative stress, improve the immunity function, and ultimately, extend lifespan (23). Antioxidants are generally the chemicals for assessment of the oxidative stress status that can be divided into reactive oxygen species, ROS diluents or antioxidant chemicals and transcription factors regulating ROS production. It is difficult to evaluate oxidative stress in different diseases by similar markers or biomarkers because the markers used in a particular disease are limited and must always be carefully filtered (14). They contain a variety of antioxidants as counter-attacking agents on both sides of their membranes. In the physiological response, the body must be able to defend itself against oxidative stress through two physical and chemical processes.

Physical defense is the limiting of the free radicals activity in their production sites within the cell. Enzymes that can neutralize the dangerous forms of reactive oxygen are considered the physical defense. Enzymatic and non-enzymatic antioxidants defense shows a serious role in the preserving of normal ROS levels. Vitamin A, C and E can disrupt the primary chain reactions by giving electrons to free radicals (24). DNA care is another of the body's intracellular defenses against oxidative damage. Although the complex stress responses with proteins and cell membranes can trigger the process of cell suicide (apoptosis) (25). One of the cellular oxidative damages is DNA damage and cytotoxicity; so many studies are under way to develop new methods and strategies in the prevention and treatment of cancer. However, the variations of the mitochondrial genome and dysfunction have been increasingly recognized as a significant donor in PCOS, CVD and cancer. For example, the mitochondrial DNA mutations can be the other target of assesments on PCOS heritability (26).

2.5. How does oxidative stress profile?

Today, the relationship between oxidative stress and chronic diseases such as: cardiovascular disease (CVD) (27), type2 diabetes (28), psychological disease (29), cancer (30), PCOS (31), Alzheimer (32), Multiple sclerosis (MS) (33) and other diseases have been identified.

Many different components and factors that produced in oxidative stress can be investigated. This assessment is called Oxidative Stress Index (OSI). This index is a new strategy for

represents the oxidative stress status in the disease process. OSI is beneficial for investigation and management in clinical medicine (34). So, several indexes have been suggested for measuring of OS in humans includes: Oxidative Stress Index (OSI), Oxidative Stress Score (OSS), Glutathione Ratio (GSSG/GSH), Tiol Ratios (-SH/TT, -SS/-SH, and-SS/TT), and OXY-index (35). All of oxidative stress index parameters are significantly higher in women with PCOS than controls. Also, fetuin-A levels as an indicator for IR in serume of PCO patients is higher in the PCOS group than control (36, 37).

3. Polycystic ovary syndrome (PCOS) and oxidative stress (OS)

Polycystic ovary syndrome (PCOS) as a chronic heterogeneous disease is often associated with insulin resistance (IR), hyperandrogenism, chronic inflammation and oxidative stress (OS) (4). Many studies have shown that the level of operating system of oxidative stress in PCO women is significantly higher than normal subjects. This assessment of the oxidative stress status has been performed by using of circulating markers of PCO wome such as malondialdehyde (MDA) in serum and erythrocyte (38) are higher than normal women. Superoxide dismutase (SOD) in serum, erythrocyte and follicular floid (39) is higher than normal like Xanthine oxidase (XO) in serum of these patients (40). But glutathione peroxidase (GPX) (41) and 8-Hydroxydeoxyguanosine (8-OHdG) in serm of women with PCO are lower than normal women (42). These markers are suitable for assessment of oxidative stress in PCOS (43). The levels of operating system of the oxidative stress are significantly associated with factors such as obesity (44), insulin resistance (IR) (45), androgens (46), and chronic inflammation (47). Studies of the last two decades show that reactive oxygen species (ROS) in follicular fluid, granulose and mononuclear cells (48, 49), total oxidant status (TOS) and finally oxidative stress index (OSI) in serum of PCO women are higher than normal women (50, 51).

Although oxidative stress has been recognized as a potential motive in polycystic ovarian pathology, it is still unclear whether abnormal oxidative stress levels in patients with PCOS are the cause of this syndrome or are directly related to its potential complications?

3.1. Relationship between polycystic ovary syndrome (PCOS) and oxidative stress (OS)

3.1.1. Sympathetic nervous system (SNS), PCOS and OS:

There are many factors between the complications of PCOS and the hyperactivity of the SNS (52). The anatomical findings in animals (53) and humans (54) confirm an increase of the chatecolamine nerve fibers in the ovaries. One of the most potent markers for the SNS activity is nerve grough factor (NGF). Dissen et al. showed that the ovarian NGF is higher than normal subjects in the modeling mice and women with PCO (55) but serum NGF was significantly lower in these women (56). Kishi et al. (2012) reported that oxidative stress in the brain is an important factor for regulating of SNS activity and therefore, this is can be the major cause of hypertension (57). PCOS is associated with 1) metabolic disorders (58), 2) the high risk of cardiovascular disease (CVD) (59) and 3) diabete in the context of overactivity of SNS (4). The hyperactivity of SNS in both PCOS and metabolic syndrome (MetS) are associated with the involvement of two ADR-α2 (60) and ADR-β2 (61).

The role of central noradrenaline (NA) is very important in the brain-ovary axis. Cerebral NA originates from the Locus coeruleus (LC) neucleus as the smallest neucleus in the midebrain organization. LC is the important site for the largest accumulation of NA neurons that adjacent to the fourth ventricle in the brain bridge or pontine. Our study in 2012 showed that chemical degradation of the LC neucleus in the PCO modeling rats changes the follicle's morphology. These morphologic polycystic ovary (PCOM) changes included a small size of antral follicles and hypertocosis (enlarged thecal cells) (62). Another important role of NA in the brain-ovary axis is control of LH surge. LH surge is begun by a dramatic elevation of estradiol production by the preovulatory follicle. The LH surge stimulates the luteinization process in granulosa cells and also stimulates the synthesis of progesterone responsible to the midcycle FSH surge. LH hypersecretion in PCO women is probably due to enhanced sensitivity of pituitary to gonadotropin releasing hormone (GnRH) or changes

in pattern of GnRH secretion. Therefore, changed production of sex steroid, metabolic dysfunction, and obesity could be all contribute to the changes in the pattern of LH secretion (63). Changes in LH surge pattern in brain-ovary axis and elevated level of NA metabolites in the urine of women with PCO suggest an overactivity of SNS that has been demonstrated in animal and human studies (64). By increasing the activity of ovarian SNS, catecholamine homeostasis is altered and leads to a selective down-regulation of beta-adrenoceptor at the level of interestitial cells in thecal layer and suppresses the activity of this adrenoceptor in the ovary (65).

The insulin signaling pathway as a metabolic process in PCOS is directly related to the level of SNS activity. Desai and et al in 2014, reported that lipid peroxidation (MDA) and total antioxidant capacity (TAC) as indicators of antioxidant status with fasting blood glucose, insulin, and uric acid in non-obese patients with PCO accompanied significant changes in both study and control groups (66). Bañuls et al in 2017 suggested that polycystic ovary syndrome is associated with insulin resistance, which can also lead to metabolic syndrome (MetS). Therefore, oxidative stress and leukocyte-endothelium interactions are PCOS-dependent and thus their results support this hypothesis that there is a correlation between metabolic changes, increased ROS production, endoplasmic reticulum stress, and leukocyte-endothelium interactions in PCOS that ofcourse all of these events can lead to cardiovascular complications (67).

3.1.2. Insulin resistance (IR), PCOS and OS:

Insulin resistance (IR) was first introduced in 1960 by Dr. Yalo and Bresson.

IR is a metabolic state with too much insulin production against the normal response, because insulin sensitivity reduces under such conditions. Then this resistance can reduce the insulin response to the all of metabolic effects in the body. One of the most important features of PCOS is type2 diabetes with IR, which is associated with obesity and CVD (68). Insulin in the brain performs metabolic, neurotropic, neuromodulatory and neuroendocrine functions. Energy homeostasis is one of the important metabolic and neuromodulatory functions of brain's insuline (69). Insulin is a potent neuromodulator in the energy homeostasis and studies have shown that injecting of insulin antibody into the intermedia nucleus of the rat's hypothalamus causes overeating and obesity (70, 71). In this brain response, insulin supplies intracerebral energy and then stores it into neurons. This energy production pathway is accompanied by activation of ADR- β and the detachment or extrusion of glucose from glycogen stores of brain glial cells that occur within astrocytes. Then, by converting astrocytic glycogen into glucose, the glucose is stimulated by insulin via glucose carrier (GLUT1) and transferred to the extracellular fluid. This glycogen is actually an additional source of energy for the neurons which is dependent on the SNS. These results indicate 1) sensitivity rate of brain tissue to the both glucose and insulin and 2) an important role of NA on homeostasis processes (72). IR in the obese PCO women can disrupt the synthesis of androgens or through the adipocytokines can directly or indirectly, affect on the brain-ovarian axis. Therefore, it affects on the hypothalamic secretion and the peripheral metabolism of steroids (73). Studies have shown that CVD (74), diabetes (75), sleep apnea or respiratory arrest (76), polycystic ovary syndrome (77, 42), and metabolic syndrome (78) are all associated with the overactivity of SNS (79). A meta-analysis of PCOS confirms the presence of PCOS-related insulin resistance (IR) and metabolic syndrome in non-obese patients (80) and obese women (81).

3.1.3. Hyperandrogenism, PCOS and OS

Hyperandrogenism is a prominent feature of PCOS. Testosterone level in women with PCO is usually higher than normal women. Codner's hypothesis in 2009, was based on the prevalence of type1 diabetes in patients with PCO which; both ovaries and adrenals are exposed to high androgen and insulin levels and the PCO is a frequent complaint of the women with Type1 diabetes (82). The abnormal gonad's steroidogenic activity that observes in patients with PCO is due to the high level of androgen in the ovaries that inhibits follicular maturation and helps to the negative process in ovulation. Hyperandrogenemia

itself can cause the desensitization of hypothalamous response to progesterone/estrogen negative feedback system which; further increases the secretion of GnRH and ovarian androgen production (83).

Studies in the culture medium show that, steroidogenesis activity of single cells in PCO women is higher than in the control group. Increased levels of androgen secretion increased the activity of the enzymes after repeatedly culturing the cells. Thus, this hyperandrogenism produced the combination of testosterone, such as β3-hydroxy dehydrogenase, CYP17 and CYP11A (73). Hyperandrogenism and oxidative stress are associated in PCOS (49), but we do not know whether the hyperandrogenism can activate oxidative stress in PCO women or not.

4. Metabolic syndrome and oxidative stress

Reproductive and metabolic disorders are associated with PCOS. These disorders are more common in obese people. Reports suggest that metabolic syndrome, similar to PCOS, is associated with insulin resistance (IR). IR may be a suitable central and peripheral stimuls for the other disorders in the two syndromes (74, 80). IR can via overproducing of insulin, can reduce the capacity of beta cells and predispose the patient to type2 diabetes. IR may also damages insulin-sensitive organs, including liver and kidney. The hyperinsulinemia reflex can transmit triglycerides from the liver into the bloodstream, thereby lowering HDL and increasing LDL cholesterol levels. Dyslipidemia (HDL/LDL imbalance) as one of the factors of metabolic syndrome can easily increase the risk of CVD by free radical invasion especially in the case of triglycerides, because it has not been neutralized via antioxidants. As a result, this imbalance between oxidants and antioxidants can lead to lipid peroxidation under oxidative stress, and may be an effective factor in the development of atherosclerosis and CVD risk (coronary artery disease, stroke, and peripheral vascular disease) (81).

Mitochondria and ATP/NA in ovary

The electron transport chain activity products are both mtROS and adenosine 5'-triphosphate (ATP) which ATP as a major intracellular energy (powerhouse) basis is an excitatory cotransmitter for the autonomic nerves system (ANS). ATP through oxidative phosphorylation is colocalized with NA in the vesicles of synaptic's cleft at the postganglionic sympathetic nerves (27). The ratio of ATP to NA differs between different sympathetic nerve fibers. These nerves change through growth and in some pathological conditions, like hypertension. ATP as a cotransmitter and NA have a synergistic actions in the postjunctional (28).

Intercellular messengers (para-crine-signaling) are very critical in ovarian physiology for follicugenesis and streiogenesis. The purinergic system (ATP) is one of the vital intra-ovarian modulator, because it can regulate proliferation, steroidogenesis and apoptosis processes in the response to gonadotropic hormones (GnRH) (29). Several P2 receptors with essential roles have been found in the ovary. Wang and et al., (2015) showed P2X7 receptor was exactly expressed on the porcine ovarian thecal and murine luteal cells and the activation of P2X7 decreased cell proliferation and encouraged apoptosis via calcium-dependent manner (30). Luteal phase deficiency (LPD) is a majour cause for female infertility and nucleotides receptors (P2) can be released of sympathetic nerve ending and be influential on the corpus luteum function. Therefore, exploring of purinergic signaling and SNS (ATP/NA) in luteal cells can be having suggestions for treatment of the luteal phase inadequacy. In the luteal phase the corpus luteum (CL) is made by the luteinizing hormone (LH) function on the mature preovulatory follicle. CL is a transitory endocrine gland that is vital for mammalian's pregnancy. There is the continual dependency in the primate CL on LH/CG/cAMP which seems to trigger luteolysis that can provide by the endogenous LH pulses (31). Acquisition of LH receptor (LHR) by preovulatory granulosa cells results from estrogen-stimulated and FSH-stimulated transcription of the LHR gene,

the actions of which are mediated largely by intracellullar cyclic adenosine monophosphate (cAMP).32

In women with PCOS, infertility could result from the corpus luteum (CL) dysfunctional (32).

Recent developments of the inflammatory triggers in women with PCO show the innate immune responses. PCOS is a chronic low-grade inflammation disease (27) which was associated by metabolic abnormalities like IR that has a potent link with chronic inflammation which were higher in overweight PCO patients (28).

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