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HYROIDITIS AS ARISK FACTOR IN POLYCYSTIC OVARIAN SYNDROME WOMEN

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Abstract:

Oxidative stress (OS) is a condition that occurs as a result of an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify and neutralize them.It can play a role in a variety of reproductive system conditions, including polycystic ovary syndrome (PCOS), endometriosis, preeclampsia, and infertility. In this review, we briefly discuss the links between oxidative stress and PCOS. Mitochondrial mutations may lead to impaired oxidative phosphorylation (OXPHOS), decreased adenosine triphosphate (ATP) production, and an increased production of ROS. These functional consequences may contribute to the metabolic and hormonal dysregulation observed in PCOS. Studies have shown that OS negatively affects ovarian follicles and disrupts normal follicular development and maturation. Excessive ROS may damage oocytes and granulosa cells within the follicles, impairing their quality and compromising fertility. Impaired OXPHOS and mitochondrial dysfunction may contribute to insulin resistance (IR) by disrupting insulin signaling pathways and impairing glucose metabolism. Due to dysfunctional OXPHOS, reduced ATP production, may hinder insulin-stimulated glucose uptake, leading to IR. Hyperandrogenism promotes inflammation and IR, both of which can increase the production of ROS and lead to OS. A detrimental feedback loop ensues as IR escalates, causing elevated insulin levels that exacerbate OS. Exploring the relations between OS and PCOS is crucial to fully understand the role of OS in the pathophysiology of PCOS and to develop effective treatment strategies to improve the quality of life of women affected by this condition. The role of antioxidants as potential therapies is also discussed.

Keywords: oxidative stress; polycystic ovary syndrome; oxidative phosphorylation; reactive , oxygen species

التهاب الغدة الدرقية كعامل خطر في متلازمة المبيض المتعدد الكيسات لدى النساء

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خلاصة:

الإجهاد التأكسدي (OS) هو حالة تحدث نتيجة عدم التوازن بين إنتاج أنواع الأكسجين التفاعلية (ROS) وقدرة الجسم على إزالة السموم وتحييدها. ويمكن أن يلعب دورًا في مجموعة متنوعة من حالات الجهاز التناسلي، بما في ذلك متلازمة المبيض المتعدد الكيسات(PCOS) ، بطانة الرحم، تسمم الحمل، والعقم. في هذه المراجعة، نناقش بإيجاز الروابط بين الإجهاد التأكسدي ومتلازمة تكيس المبايض. قد تؤدي طفرات الميتوكوندريا إلى ضعف الفسفرة التأكسدية(OXPHOS) ، وانخفاض إنتاج الأدينوزين ثلاثي الفوسفات (ATP)، وزيادة إنتاج .ROS قد تساهم هذه العواقب الوظيفية في خلل التنظيم الأيضي والهرموني الذي لوحظ في متلازمة تكيس المبايض. أظهرت الدراسات أن نظام التشغيل يؤثر سلبًا على بصيلات المبيض ويعطل التطور والنضج الجريبي الطبيعي. قد يؤدي الإفراط في أنواع الأكسجين التفاعلية إلى إتلاف البويضات والخلايا الحبيبية داخل البصيلات، مما يؤدي إلى إضعاف جودتها والإضرار بالخصوبة. قد يساهم ضعف OXPHOS وخلل الميتوكوندريا في مقاومة الأنسولين (IR) عن طريق تعطيل مسارات إشارات الأنسولين وإضعاف استقلاب الجلوكوز. بسبب خللOXPHOS ، فإن انخفاض إنتاجATP ، قد يعيق امتصاص الجلوكوز المحفز بالأنسولين، مما يؤدي إلى الأشعة تحت الحمراء. يعزز فرط الأندروجينية الالتهاب والأشعة تحت الحمراء، وكلاهما يمكن أن يزيد من إنتاج أنواع الأكسجين التفاعلية ويؤدي إلى نظام التشغيل. تنشأ حلقة ردود فعل ضارة مع تصاعد الأشعة تحت الحمراء، مما يتسبب في ارتفاع مستويات الأنسولين التي تؤدي إلى تفاقم نظام التشغيل. يعد استكشاف العلاقات بين نظام التشغيل ومتلازمة تكيس المبايض أمرًا بالغ الأهمية لفهم دور نظام التشغيل بشكل كامل في الفيزيولوجيا المرضية لمتلازمة تكيس المبايض ولتطوير استراتيجيات علاجية فعالة لتحسين نوعية حياة النساء المصابات بهذه الحالة. ويناقش أيضا دور مضادات الأكسدة كعلاجات محتملة.

الكلمات المفتاحية: الإجهاد التأكسدي؛ متلازمة المبيض المتعدد الكيسات؛ الفسفرة التأكسدية؛ أنواع الاكسجين التفاعلية

1. Introduction

Oxidative stress (OS), or an imbalance between oxidants and antioxidants, is related to the generation of excessive amounts of reactive oxygen species (ROS) and the body's ability to defend against their damaging effects with antioxidants, which cause DNA damage and/or cell apoptosis, affect gene expression and the immune response [1]. Importantly, OS plays a key role in the pathophysiology of a variety of gynecological disorders, including polycystic ovary syndrome (PCOS), endometriosis, unexplained infertility, and preeclampsia [2,3]. PCOS is a common hormonal disorder, according to World Health Organization (WHO) data—with the prevalence of between 8% and 13% depending on the population studied [4]. It affects mostly women of reproductive age. It is characterized by a combination of symptoms associated with hormonal imbalances, menstrual irregularities, and thepresence of excessive amounts of follicles in ovaries. The exact cause of PCOS is not fully understood, but it is believed to encompass a combination of genetic and environmental factors [5]. The diagnosis of PCOS is based on specific criteria established by the Rotterdam criteria or the Androgen Excess and PCOS Society (AE-PCOS Society) criteria [6]. For a diagnosis of PCOS according to the Rotterdam criteria, at least two out of three of the following must be met: 1. The

presence of irregular menstrual cycles, which can include oligomenorrhea (infrequent periods) or amenorrhea (absence of periods); 2. Clinical signs of androgen excess, such as hirsutism, acne, or male-pattern baldness and/or laboratory evidence of elevated androgen levels; and 3. The presence of multiple small cysts in the ovaries, as visualized on ultrasound examination [6]. PCOS may occur in four different phenotypes or subtypes defined by specific clinical features and hormonal profiles [7]. Classic phenotype is characterized by the presence of both hyperandrogenism and chronic anovulation. Women with classic phenotype typically exhibit symptoms connected with excessive androgen levels such as hirsutism (excessive hair growth), acne, and menstrual irregularities. In contrast, women with ovulatoryphenotype exhibit normal ovulatory function and no chronic anovulation. However, they may still present symptoms of hyperandrogenism, such as hirsutism or acne. This phenotype is diagnosed based on the presence of hyperandrogenism in the absence of anovulation [8]. Non-hyperandrogenic phenotype is characterized by the occurrence of chronic anovulation without significant signs of hyperandrogenism [9]. The last, nonobese phenotype is found in women who develop PCOS but do not meet the criteria for obesity [9]. Treatment options for PCOS may include lifestyle modifications such as weight loss, exercise, and a healthy diet, medications including hormonal contraceptives with antiandrogen activities, metformin, and anti-androgens, and fertility treatment for women who wish to conceive. Managing PCOS may help improve overall health outcomes and prevent long-term complications associated with the disorder, especially in older ages [10]. The current review summarizes some links between OS and PCOS.

2. ROS Production

Mitochondria, the energy-producing organelles, are a major source of ROS. In PCOS, mitochondrial dysfunction was observed, leading to an increased ROS production. ROS play a dual role, acting as both beneficial signaling molecules and potentially harmful oxidative agents when their levels become excessive. ROS are primarily generated as byproducts of cellular respiration, particularly during the electron ransport chain in mitochondria. This is a natural and essential process for energy production in cells. ROS encompass a range of molecules, including superoxide anion (O2), hydroxylradical (OH□), singlet oxygen, hydrogen peroxide (H2O2), organic hydroperoxide (ROOH), alkoxy and peroxy radicals (RO and ROO), hypochlorous acid (HOCl), and peroxynitrite (ONOO) [11,12]. In a healthy state, the production of ROS is balanced by the body's antioxidant defense systems. These antioxidants include enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), as well as non-enzymatic molecules such as glutathione and vitamins C and E [13,14]. This balance is

crucial. ROS are involved in various aspects of ovarian physiology, serving as secondary messengers in cellular signaling pathways. ROS play a nuanced role in ovarian physiology, where controlled levels of ROS are essential for normal ovarian function. However, an imbalance in ROS production and antioxidant defenses can lead to OS, which may have detrimental effects on reproductive outcomes. They play roles in regulating key ovarian processes, including meiosis, which is essential for the development of mature oocytes; ovulation, where ROS participate in the signaling cascades that trigger the release of the mature egg; and corpus luteum maintenance and regression [15]. The specific mechanism of ROS production in PCOS is not fully understood, but several factors contribute to increased ROS production in individuals with PCOS. When mitochondria are not functioning optimally, they generate more ROS as a byproduct of the electron transport chain during oxidative phosphorylation (OXPHOS). This excess ROS production contribute to OS in ovarian tissues [16]. In addition, numerous individuals with PCOS develops insulin resistance (IR). In patients with IR, hyperglycemia leads to an upsurge in the production of ROS through a NADPH oxidase p47(phox) component [17].

Furthermore, hyperglycemia promotes the release of tumor necrosis factor-alpha (TNF), a well-known contributor to IR, from mononuclear cells. It also enhances the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-_B) [18]. NF-_B, in turn, exacerbates OS by stimulating NADPH oxidase, which amplifies ROS production and sustains the inflammatory response [19]. Hyperandrogenemia heightens the sensitivity of white blood cells to hyperglycemia and aggravate OS [20]. Additionally, NADPH oxidase plays a critical role in generating ROS in individuals with obesity. In adipocytes, increased levels of fatty acids trigger OS by activating NADPH oxidase [21].OS itself perpetuate further ROS production. Damage cellular components, including DNA, proteins, and lipids resulting ROS production, trigger cellular responses that generate more ROS as a protective mechanism, creating a feedback loop of OS [22,23]. It has also been noted that some women with PCOS have reduced antioxidant defense mechanisms, which can lead to an imbalance between ROS production and ntioxidant defense, resulting in increased OS [24,25]. In addition, an imbalance in luteinizing hormone (LH), folliclestimulating hormone (FSH), and other reproductive hormones can affect ovarian function and may contribute to ROS production [26]. Lipid peroxidation (LPO) is a biochemical process in which reactive substances such as free radical's target lipids, particularly those containing carbon–carbon double bonds, notably polyunsaturated fatty acids (PUFAs) [27]. Damage to cellular structures, including cell membranes, as a result of PUFA-induced OS, leads to the accumulation of LPO products such as malondialdehyde

(MDA) and the hydroxyl radical. This heightened OS often results in increased levels of ROS in the bloodstream [11]. In PCOS, alterations in the LPO processes appear to be compensatory mechanisms, which is evident through an increase in the concentrations of antioxidants such as _-tocopherol and retinol [28]. Additionally, there is a modest reduction in the activity of SOD enzyme responsible for combating OS. These adaptations may serve to counteract the elevated OS associated with PCOS and help maintain cellular integrity and function [28,29]. LPO potentially affect the quality of oocytes. High levels of OS and LPO may lead to DNA damage in oocytes, which can reduce fertility and increase the risk of miscarriage [30].

3. Mitochondrial DNA Damage

Elevated ROS may cause damage to mitochondrial DNA (mtDNA) and impair cellular energy production, contributing to metabolic and hormonal abnormalities seen in PCOS. Mitochondria are controlled both by mitochondrial and nuclear genomes. MtDNA is circular and double-stranded. It comprises a molecule which is 16,569 bp in length and encodes 22 tRNAs, 2 rRNAs and 13 polypeptides that are essential for adenosine triphosphate (ATP) production [31,32]. Unlike nuclear DNA, which is located in the cell nucleus and inherited from both parents, mtDNA is inherited in a maternal pattern only [33]. Due to its unique inheritance pattern, mtDNA may be used to trace maternal lineages and study human population genetics. It is less prone to recombination and has a higher mutation rate compared to nuclear DNA, making it useful for analyzing evolutionary relationships and population history [31,34]. Any defects at the level of mtDNA replication affect the formation of numerous mutations, whereas mtDNA exhibits a lack of histone protection and a DNA damage repair system [35]. Indeed, previous studies showed that mtDNA mutations contributed to numerous diseases, including PCOS [36]

ovary syndrome (PCOS). (A). Mitochondria are the energy-producing structures in cells. The close proximity of mitochondrial DNA (mtDNA) to the source of reactive oxygen species (ROS) production and the limited protective mechanisms in mitochondria contribute to its susceptibility to oxidative damage and can result in various types of mutations. (B). Ovulation is a crucial event in the menstrual cycle, where a mature egg is released from the ovary, ready for potential fertilization. In small amounts, ROS are essential for normal physiological processes; however, excessive production of ROS, meaning oxidative stress (OS), can be harmful to cells and tissues. The reduction in the rate of ovulation and prevention of cumulus expansion observed after antioxidant administration might be due to the antioxidants' neutralizing effects on ROS and disruption of the delicate balance required for successful ovulation and cumulus expansion. The

citric acid (TCA) cycle is a fundamental metabolic pathway that generates energy. Citrate formation is crucial for oocyte competence process. In the oocytes of DHEA-induced PCOS mice, TCA, glucose-6-phosphate dehydrogenase (G6PD) activity, and lipid content is decreased, suggesting abnormal metabolism in the TCA cycle and the pentose phosphate pathway (HMP Shunt), which could negatively impact oocyte function. (C). Decreased oxidative phosphorylation (OXPHOS) activity is associated with the deficiency of NADH: ubiquinone oxidoreductase (Complex I, CI). Insulin plays a crucial role in regulating OXPHOS activity. It affects mitochondrial function by influencing the electron transport chain and ATP production. Increased ROS production can have a negative impact on insulin sensitivity, leading to insulin resistance. (D). Mitochondrial uncoupling protein 1 (UCP1) allows protons to re-enter the mitochondrial matrix, uncoupling the OXPHOS process from ATP production and releasing energy as heat (non-shivering thermogenesis). In women with PCOS, reduced brown adipose tissue (BAT) function was observed, which may be attributed to high androgen levels.

Figure 1. Schematic presentation of the associations between oxidative stress (OS) and polycystic

ovary syndrome (PCOS). (A). Mitochondria are the energy-producing structures in cells. The close proximity of mitochondrial DNA (mtDNA) to the source of reactive oxygen species (ROS) production and the limited protective mechanisms in mitochondria contribute to its susceptibility to oxidative damage and can result in various types of mutations. (B). Ovulation is a crucial event in the menstrual cycle, where a mature egg is released from the ovary, ready for potential fertilization. In small amounts, ROS are essential for normal physiological processes; however, excessive production of ROS, meaning oxidative stress (OS), can be harmful to cells and tissues. The reduction in the rate of ovulation and prevention of cumulus expansion observed after antioxidant administration might be due to the antioxidants' neutralizing effects on ROS and disruption of the delicate balance required for successful ovulation and cumulus expansion. The citric acid (TCA) cycle is a fundamental metabolic pathway that generates energy. Citrate formation is crucial for oocyte competence process. In the oocytes of DHEA-induced PCOS mice, TCA, glucose-6-phosphate dehydrogenase (G6PD) activity,

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mitochondrial function by influencing the electron transport chain and ATP production. Increased ROS production can have a negative impact on insulin sensitivity, leading to insulin resistance.(D). Mitochondrial uncoupling protein 1 (UCP1) allows protons to re-enter the mitochondrial matrix, uncoupling the OXPHOS process from ATP production and releasing energy as heat (non-shivering thermogenesis). In women with PCOS, reduced brown adipose tissue (BAT) function was observed, which may be attributed to high androgen levels. The following seven variants in genes encoding mt-tRNA genes were identified in women with PCOS: tRNAGln (MT-TQ), tRNACys (MT-TC), tRNAAsp (MT-TD), tRNALys (MT-TK), tRNAArg (MT-TR), tRNAGlu (MT-TE), and tRNASer (UCN) (MT-TS1), in addition to seven variants in the 12S rRNA and three variants in 16S rRNA genes [37,38]. It is suggested that mutations affecting highly conserved nucleotides such as found in the mt-tRNA or OXPHOS complex genes, critical for their stability and biochemical function, may lead to mitochondrial dysfunction and are likely to be involved in the pathogenesis of PCOS [37,38].For years, a team of Chinese researchers looking for mutations in mtDNA had repeatedly shown that mitochondrial dysfunction caused by mt-tRNA mutations mightbe involved in the pathogenesis of PCOS-IR [39,40]. The nine mt-tRNA mutations were shown that were potentially associated with PCOS-IR: tRNALeu (UUR) (MT-TL1) A3302G and C3275A mutations, tRNAGln (MT-TQ) T4363C and T4395C mutations, tRNASer (UCN) (MT-TS1) C7492T mutation, tRNAAsp (MT-TD) A7543G mutation, tRNALys (MT-TK) A8343G mutation, tRNAArg (MT-TR) T10454C mutation and tRNAGlu (MT-TE) A14693G mutation. A south Indian female population showed a significant association between D310 and A189G variants in the mtDNA D-loop region, which is much more variable and noncoding,and the reduction in mtDNA copy number (mtCN) in PCOS group compared to the controls [41]. Conversely, in the Korean population mtCN was significantly lower inwomen with PCOS compared to the controls. The correlation was negative for IR and positive for sex hormone–binding globulin (SHBG) levels [42].It is important to recognize that mitochondrial mutations are just one aspect of mitochondrial dysfunction and are not widely recognized as the primary cause of PCOS.The majority of PCOS cases are considered to involve complex genetic, hormonal, and environmental factors [43].

4. Oxidative Stress and PCOS

The first studies demonstrating elevated levels of OS and reduced antioxidant capacity in women with PCOS were published more than 20 years ago [44]. The finding was particularly relevant in women with obesity-associated PCOS phenotype, hyperandrogenism or the development of metabolic syndrome [45–47]. In addition, an in vitro study showed that OS increased the activity of ovarian

steroid-producing enzymes and stimulated androgen production [48]. The process of ovulation involves the rupture and release of the dominant follicle from the ovary into the fallopian tube, whe re fertilization may occur [49]. The regulation of ovulation is influenced by the fluctuating levels of gonadotropic hormones, especially FSHand LH, which are released by the pituitary gland [49]. The ovulation process is the key phase of the menstrual cycle [50]. It follows the follicular phase, during which the dominant follicle develops and matures under the influence

of FSH. The dominant follicle then releases the egg in response to LH surge, marking the occurrence of ovulation. Following ovulation, the luteal phase begins, characterized by the formation of the corpus luteum from the remnants of the ruptured follicle. The corpus luteum produces progesterone, which helps prepare the uterine lining for a potential implantation of a fertilized egg. If fertilization and implantation do not occur, the corpus luteum degenerates, leading to a decline in progesterone levels [51]. This hormonal shift triggers the shedding of the uterine lining, resulting in menstruation. The timing of ovulation within the menstrual cycle is typically around 14 days before the start of menstruation in a regular, 28-day cycle. However, it is important to note that the duration of the menstrual cycle and the timing of ovulation may vary among individuals. Factors such as stress, hormonal imbalances, and certain medical conditions, including PCOS, may disrupt the normal regulation of ovulation [51]. Some authors described the involvement of ROS in the ovulation process. Elevated secretion of LH in the lead-up to ovulation triggers the release of inflammatory substances within the ovary [52]. This, in turn, leads to an overproduction of ROS. Increased ROS levels play crucial roles in key aspects of the ovulation process, including cumulus expansion, progesterone production, expression of preovulatory genes and activation of ovulatory signals [53]. The interplay between ROS and SOD in the corpus luteum is pivotal in determining the duration and efficiency of progesterone production [54]. Enhanced SOD activity acts as a protector against ROS-induced damage, while reduced SOD activity can lead to ROS-triggered apoptosis and the regression of the corpus luteum. These dynamics highlight the central roles of ROS and SOD in governing

6. Conclusions

While the association between OS and PCOS is increasingly recognized, further research is needed to fully elucidate the role of OS in PCOS pathophysiology. Investigating the mitochondrial function, ATP production, and OXPHOS efficiency in PCOS may provide further insights into the metabolic and hormonal deregulation associated with the condition. Various antioxidants, such as NAC,

vitamin E, and alpha-lipoic acid, have been proposed as potential therapeutic agents to reduce OS and improve metabolic and reproductive outcomes in women with PCOS. Lifestyle interventions, including exercise and dietary modifications, have also been shown to reduce OS and improve insulin sensitivity and fertility in PCOS patients. Understanding the links between OS and PCOS is crucial formproving lipid metabolism [105–107]. developing effective treatment strategies to improve the quality of life of women affected by this condition.

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