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Polycystic ovary syndrome (PCOS) and oxidative stress

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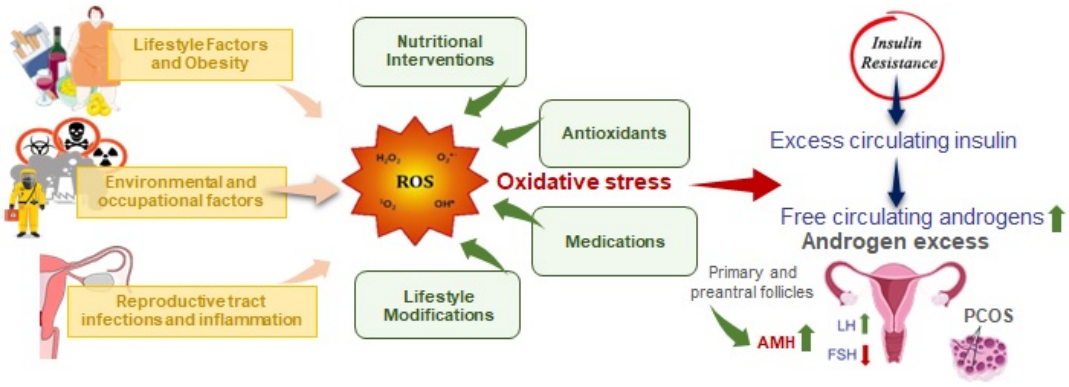
Review

ABSTRACT



Polycystic Ovary Syndrome (PCOS) affects about 10% of women of reproductive age, characterized by hyperandrogenism, anovulation, and polycystic ovaries. Despite extensive research, its etiology remains uncertain with genetic, metabolic, and environmental factors implicated. This review explores the relationship between PCOS and oxidative stress (OS), focusing on molecular pathways and their effects on reproductive physiology. OS arises from an imbalance between reactive oxygen species (ROS) production and the intricate endogenous antioxidant defenses, causing cellular damage. Recent studies show heightened oxidative conditions in PCOS women, potentially exacerbating hormonal imbalances, inflammation, and insulin resistance. The elevated ROS generation, combined with diminished antioxidant defense in PCOS patients, links to compromised oocyte health, abnormal follicle growth, and endometrial issues. Interventions such as antioxidant supplementation and lifestyle alterations show promise in re-establishing oxidative balance, improving symptoms, and improving fertility. This review consolidates contemporary insights into the crosstalk between PCOS and OS, emphasizing prospective treatment pathways and the importance of further explorations to elucidate this intricate interconnection.

Keywords: androgens; female infertility; insulin resistance; oocyte quality; oxidative stress; polycystic ovary disease

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a predominant endocrine anomaly, affecting roughly 10% of females in their reproductive years globally.[1, 2] It is distinguished by a diverse array of clinical manifestations, including inconsistent menstrual periods, elevated androgen levels, and the ultrasonographic detection of polycystic ovaries.[3] This syndrome is linked to a wide range of metabolic and reproductive disturbances.[4] Its origin is multifarious, with genetic, environmental, and lifestyle determinants playing a role.[5] Recent scientific investigations have highlighted OS as a potential element in the underlying mechanisms of PCOS.[6]

OS, defined by a disparity between reactive oxygen species (ROS) generation and the antioxidative countermeasures, has been traditionally linked to various disease states, ranging from cardiovascular ailments to neurodegenerative conditions.[7-9] In the context of PCOS, comprehending the significance of OS is crucial due to its potential influence on both reproductive and metabolic abnormalities seen in these patients.[10] Initial research indicates heightened oxidative markers in PCOS-afflicted females, hinting at a complex interplay that might unveil new therapeutic avenues.[10]

This literature overview aims to shed light on the intricate interrelation between OS and PCOS. By synthesizing current scientific insights, we aspire to clarify the mechanistic involvement of OS in the emergence and evolution of PCOS, its repercussions on fertility, and its ties to the array of related metabolic issues.

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Additionally, our goal is to underscore potential treatment modalities focusing on this oxidative context, providing fresh optimism for countless women affected globally. Through this all-encompassing scrutiny, our ambition is to enhance the understanding of PCOS and establish a foundation for upcoming studies in this evolving domain.

DEFINITION AND PATHOPHYSIOLOGY OF PCOS

PCOS is a complex and diverse endocrine condition primarily impacting females in their reproductive years.[11] It manifests through a blend of clinical, hormonal, and anatomical indications, encompassing ovulatory disturbances, hyperandrogenic states, and the occurrence of numerous diminutive ovarian cysts.[3, 5]

Hormonal Imbalances

The underlying mechanisms of PCOS are intricate and multifarious, with hormonal imbalances being pivotal. The ovaries produce elevated quantities of androgens, notably testosterone. The augmented androgen levels arise due to (a) enhanced enzymatic function of cytochrome P450c17α in ovarian theca cells, resulting in amplified androgen synthesis[12], (b) aberrant insulin metabolism, as a significant number of PCOS-affected women manifest insulin resistance, leading to reactive hyperinsulinemia.[13] This insulin surge acts in tandem with luteinizing hormone (LH) to stimulate androgen generation in the ovaries, (c) disturbances within the hypothalamic-pituitary-ovarian (HPO) axis led to a heightened release of LH relative to follicle-stimulating hormone (FSH), endorsing theca cell function and consequently, augmented androgen synthesis.[14]

Ovulatory Disturbances

Surging androgen concentrations impede the standard evolution of follicles in the ovaries.[15] Instead of a lone follicle reaching maturity and being released during the menstrual phase, multiple follicles initiate maturation but do not attain complete maturity. This leads to anovulatory cycles, inducing menstrual inconsistencies and potential infertility. These immature follicles become the emblematic tiny cysts observed via ultrasonography, providing the ovaries their 'polycystic' nomenclature.[5, 16]

Metabolic Abnormalities

The commonality of insulin resistance in PCOS not only propels elevated androgen concentrations[12] but also augments the susceptibility of these individuals to metabolic challenges.[17] Such challenges encompass a heightened likelihood of developing type 2 diabetes mellitus, altered lipid profiles, and cardiovascular disorders.[18]

Inflammatory Indicators

Preliminary studies indicate that a mild persistent inflammatory state may be implicated in PCOS.[19] Females with PCOS frequently display heightened concentrations of inflammation-associated markers, potentially influencing both ovarian and metabolic disturbances.[20]

OXIDATIVE STRESS MARKERS IN PCOS

Reactive Oxygen Species in PCOS

PCOS is a complex endocrine disorder prevalent among many women in their reproductive years, marked by persistent anovulation, elevated androgen levels, and the presence of multiple ovarian cysts.[5, 12] While the precise cause of PCOS is still under investigation, mounting research indicates that OS, instigated by increased concentrations of ROS, has a pivotal role in its development.[6,10]

ROS are chemically active oxygen-containing molecules, examples of which include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (·OH). In normal physiological states, ROS emerge as secondary products from mitochondrial electron transport processes and are instrumental in cellular signaling and maintaining equilibrium.[21, 22] Nevertheless, when there is an overproduction or inadequate removal of ROS, OS arises, leading to harm to vital cellular structures such as DNA, proteins, and lipids.[23] In the context of PCOS, various elements might amplify ROS generation or weaken the natural antioxidant defense.[23] Insulin resistance, frequently present in individuals with PCOS, promotes ROS accumulation.[13] Chronic inflammation, commonly seen in those afflicted with PCOS, can also stimulate immune cells, further boosting ROS levels.[19] Concurrently, certain research suggests that the antioxidant defense in PCOS may be insufficient, intensifying the OS.[24] Crucially, this escalated OS can intensify the hormonal and metabolic disturbances typical of PCOS.[4] There is evidence connecting ROS to heightened androgen production, a defining feature of PCOS. Elevated ROS levels can also disrupt the activity of granulosa cells and hinder follicle maturation, leading to anovulation.[6] Furthermore, oxidative harm to the endometrial lining may impede embryo implantation, shedding light on the often-seen decreased fertility in those with PCOS.[10] Therefore, ROS and the ensuing OS are central to various detrimental pathways in PCOS. They play a role in its underlying mechanisms and accentuate many of its clinical signs.[6] Tackling OS, through changes in lifestyle, the use of antioxidants, or medicinal treatments, could present an effective strategy for managing PCOS and its related issues.

Antioxidant status in women with PCOS

Recent investigations have identified a significant alteration in the antioxidant profile of women with PCOS.[25] Specifically, these individuals display diminished levels of key antioxidants and a concomitant elevation in indicators of OS. The body's intrinsic antioxidant mechanisms comprise enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, in addition to non-enzymatic antioxidants like vitamin C, vitamin E, and glutathione. Data suggest that PCOS-afflicted women often present with diminished enzymatic antioxidant activity and lowered concentrations of non-enzymatic antioxidants.[10, 25] At the same time, markers of OS, like malondialdehyde (MDA), are discernibly elevated in the serum of these patients.[10, 26]

The complications of this disrupted antioxidant profile are diverse. OS is implicated in the onset of insulin resistance, inflammation, and endothelial dysfunction, all commonly manifesting in PCOS.[6, 19] Consequently, the potential role of antioxidants in PCOS management has drawn considerable scientific interest. Introducing exogenous antioxidants, encompassing vitamins C[27] and E[28], zinc[29], and selenium[30], has been mooted as a prospective therapeutic intervention. Preliminary evidence indicates potential improvements in hormonal dynamics and mitigation of metabolic imbalances with such treatments.[27-30]

Nevertheless, as the correlation between antioxidant status and PCOS becomes clearer, it remains imperative to delve deeper into the precise mechanisms and establish the most effective treatment modalities. Determining whether the detected OS precedes or results from PCOS will be vital in fine-tuning therapeutic strategies, potentially transitioning from mere management to prevention of the condition.

Lipid peroxidation in PCOS

Lipid peroxidation refers to the oxidative breakdown of polyunsaturated fatty acids (PUFAs), resulting in cellular membrane disruption and the generation of reactive aldehydes like MDA and 4-hydroxynonenal.[31] These reactive aldehydes are biologically active and can amplify OS and trigger inflammatory cascades.[32] Recent scientific investigations indicate that females diagnosed with PCOS display increased markers of lipid peroxidation, with MDA frequently identified in multiple studies.[33-35] The augmented OS in PCOS can be traced back to several sources. Primarily, hyperinsulinemia and insulin resistance, frequent hallmarks of PCOS, promote the formation of ROS, which instigate lipid peroxidation.[6] Additionally, the heightened androgen concentrations typical of PCOS enhance the vulnerability of lipids to peroxidative processes.[12, 36]

The consequences of intensified lipid peroxidation in PCOS are multifaceted.[34] Oxidative insults to cellular membranes can compromise the operational integrity of diverse cell populations, including ovarian granulosa cells, potentially influencing processes like folliculogenesis and steroidogenesis and aggravating the endocrine irregularities inherent to PCOS.[34] Moreover, the resultant inflammatory reactions might be linked to the elevated cardiovascular risk profiles noted in individuals with PCOS.[25] Thus, lipid peroxidation serves as a central component in the pathophysiological nexus of PCOS, bridging metabolic and reproductive dysfunctions.[34] The pronounced OS and subsequent lipid peroxidation in PCOS highlight the significance of antioxidant approaches, encompassing both nutritional and therapeutic avenues, in the clinical oversight of this condition.[33] An in-depth grasp of these mechanisms will foster the development of more precise and efficacious therapeutic modalities for PCOS in forthcoming research.

PROTEIN AND DNA OXIDATION MARKERS IN PCOS

Markers for Protein Oxidation

Protein carbonyls: The content of protein carbonyl is a universally recognized indicator of oxidative harm to proteins. Women with PCOS have shown increased protein carbonyl levels in their serum compared to healthy controls. Augmented carbonylation can modify protein functionality, induce protein cross-linking, and lead to a decline in cellular operations, potentially intensifying PCOS symptoms.[37]

Advanced oxidation protein products (AOPP): Produced from the interaction between plasma proteins and chlorinated oxidants, AOPPs act as an additional marker for oxidative damage to proteins. PCOS has been linked with elevated AOPP levels, possibly influencing the vascular issues seen in these individuals.[38]

DNA Oxidation Markers

8-Hydroxy-2'-deoxyguanosine (8-OHdG): This particular marker originates from oxidatively altered DNA bases, with guanine being

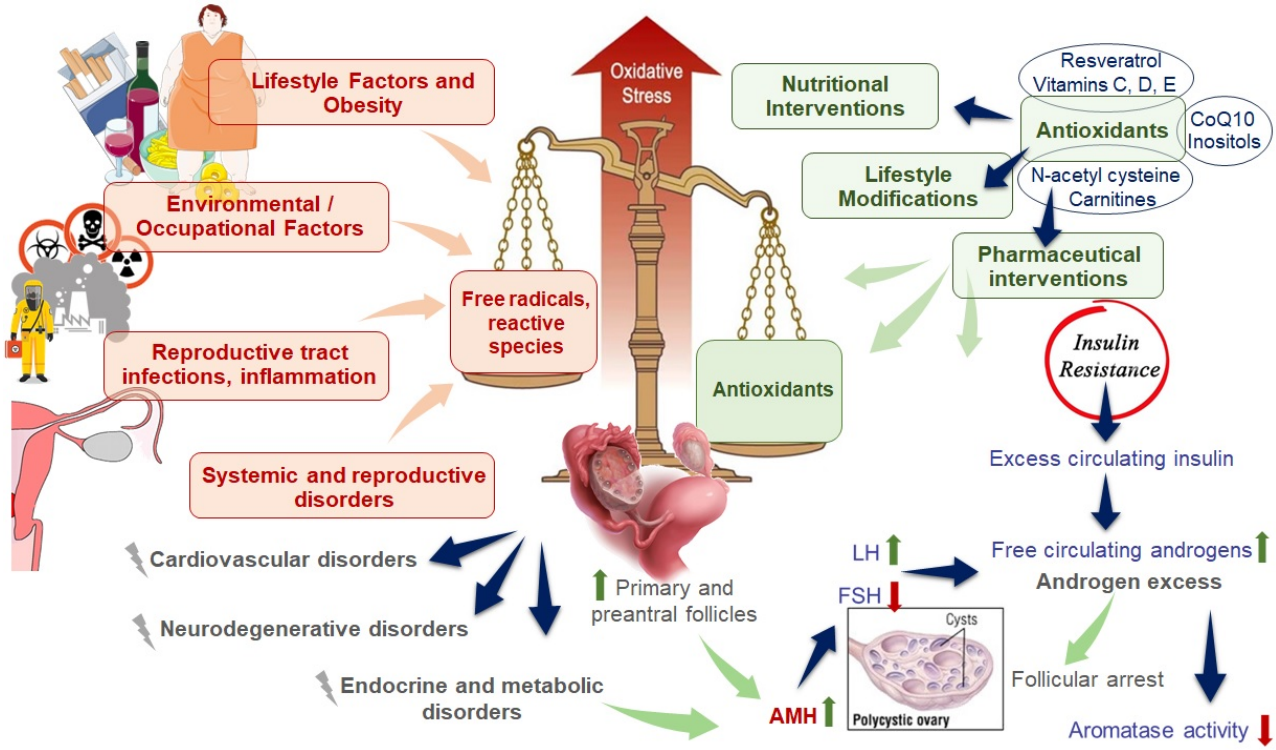

Figure 1. Mechanistic pathophysiology of polycystic ovary syndrome (PCOS) in relation to oxidative stress (OS). Role of various factors in induction of OS to cause metabolic-endocrine disturbances. Antioxidants mitigate the effects of OS and helps to reduce the deleterious effects of PCOS.

a primary target. A surge in 8-OHdG levels in urine or serum signifies DNA damage and has links to diverse diseases, such as cancers and neurodegenerative disorders.[39] Numerous research endeavors have revealed increased 8-OHdG concentrations in PCOS-afflicted women, emphasizing the extent of DNA oxidative harm in this ailment.[40]

Comet assay: Employing this adaptable technique, DNA damage, including base oxidations and strand ruptures, can be assessed. The extent of damage is visually represented by the movement pattern of DNA in an electric field: greater harm results in a more pronounced 'tail' resembling a comet. Some investigations have detected heightened DNA impairment in lymphocytes of individuals with PCOS using the comet assay, corroborating the theory of OS in PCOS pathology.[41]

Scrutinizing the significance of protein and DNA oxidation markers in PCOS can furnish insights into its underlying mechanisms, potentially facilitating diagnosis and predicting disease progression.[42] Furthermore, these markers might steer the formulation of specific therapeutic approaches. For example, antioxidant supplementation could reestablish oxidative equilibrium, possibly alleviating PCOS symptoms and minimizing the likelihood of concomitant disorders like cardiovascular ailments and type 2 diabetes.[33] Nevertheless, one must interpret these results prudently. Although OS indicators are promising, they are not exclusive to PCOS. Other diseases may also present elevated levels. Consequently, while these markers might supplement diagnostic data, they should not supplant established PCOS diagnostic standards.

MECHANISTIC LINK BETWEEN OXIDATIVE STRESS AND PCOS

Role of oxidative stress in PCOS pathogenesis

The complete pathogenesis remains elusive, but recent insights suggest significant role of OS in eliciting the ovarian abnormalities typical of PCOS.[6]

Oxidative Stress and Ovarian Morphology in PCOS

OS arises when there is a disparity between the generation of ROS and the organism's capability to mitigate their deleterious impacts using antioxidant mechanisms.[23] Ovaries from females with PCOS encounter heightened ROS concentrations, which are believed to alter the ovarian architecture.[43] Notably, research has indicated that the follicular fluid and serum of women with PCOS possess increased ROS concentrations compared to those without the condition.[44]

A defining characteristic of PCOS is the existence of numerous diminutive antral follicles that stagnate at the pre-antral or antral phases.[5] Augmented ROS levels can jeopardize oocyte quality by inciting lipid peroxidation in the membrane of oocyte, potentially leading to diminished oocyte maturation capabilities.[35] This could account for the prevalent incidence of immature oocytes in those with PCOS.[34] Additionally, the ovarian stroma in PCOS tends to be thickened and hyperthecotic. OS is postulated to foster this hyperthecosis, defined by a surge in theca cells. An excess of ROS can promote theca cell proliferation and hinder their apoptosis, resulting in an overabundance in the ovarian stroma.[45]

Oxidative Stress and Ovarian Function in PCOS

Impaired Folliculogenesis: Folliculogenesis, the evolution of ovarian follicles, is a delicate and intricately modulated process.[46] OS can interfere with folliculogenesis by triggering apoptosis in granulosa cells, stifling their proliferation, and diminishing follicular sensitivity to gonadotropins. Such disturbances may lead to anovulation, commonly seen in PCOS.[47]

Steroidogenic Disruption: In the synthesis of ovarian steroids, theca cells and granulosa cells are collaborative partners. Heightened ROS levels within the ovarian environment can misdirect steroidogenesis by altering the enzymatic routes.[48] This alteration may cause excessive androgen production, typical in PCOS.[49] Moreover, OS can impede the enzymatic transformation of androgens to estrogens in granulosa cells, contributing to the estrogen deficit noted in some PCOS-affected women.[50]

Endoplasmic Reticulum (ER) Stress and Autophagy: OS is recognized to provoke ER stress, which in turn leads to the unfolded protein response in cells.[51] When this occurs in ovarian granulosa cells, it can impede cellular operations and prompt autophagy, a cellular breakdown mechanism. In PCOS-afflicted ovaries, amplified autophagy may lead to follicular attrition and decay.[52]

Influence of oxidative stress on insulin resistance in PCOS

In the realm of clinical presentations, insulin resistance (IR) stands out as a common metabolic anomaly in patients.[17] The relationship between OS and insulin resistance in PCOS requires detailed investigation to understand the fundamental pathophysiological processes and potential treatment options.

Molecular Interactions between Oxidative Stress and Insulin Resistance in PCOS

As discussed earlier, women with PCOS exhibit increased indicators of OS, such as MDA, and reduced antioxidant agents like SOD. These oxidative alterations significantly influence insulin-mediated pathways.[33]

Insulin resistance associated with PCOS can partially be traced back to the serine phosphorylation of the insulin receptor substrate-1 (IRS-1), a consequence of amplified ROS. ROS-induced activation of stress-responsive intracellular routes, specifically the c-Jun N-terminal kinase (JNK) and the IκB kinase (IKK) pathway, culminates in this aberrant phosphorylation. Given that IRS-1 is integral to insulin signaling, its dysfunction leads to diminished glucose absorption and glycogen production, both of which are emblematic of insulin resistance.[13, 17]

Oxidative Stress, Endoplasmic Reticulum (ER) Stress, and Insulin Resistance

ER is a crucial cellular structure tasked with protein synthesis and folding. Its function can be disrupted by OS, thereby inducing ER stress.[51] Research has demonstrated that oxidative and ER stress collectively aggravate insulin resistance in PCOS. Elevated OS levels cause protein misfolding or unfolding within the ER, consequently initiating the unfolded protein response (UPR). Prolonged activation of the UPR may dampen insulin receptor signaling, leading to decreased translocation of glucose transporter type 4 (GLUT4) to the cell membrane, intensifying insulin resistance.[53, 54]

Lipotoxicity, Oxidative Stress, and Insulin Resistance

PCOS frequently exhibits symptoms of dyslipidemia, marked by an increase in circulating free fatty acids (FFAs).[55] Excessive FFAs

can disrupt mitochondrial function, resulting in inadequate fatty acid oxidation and an upsurge in ROS production. Subsequently, these ROS can stimulate kinases that obstruct insulin pathways. Furthermore, heightened FFA levels lead to the buildup of lipid derivatives like diacylglycerols and ceramides, which can activate protein kinase C (PKC). This enzyme plays a role in phosphorylating IRS-1 at serine locations, undermining insulin-mediated pathways and fostering insulin resistance.[56]

Recognizing the dynamics between OS and insulin resistance in PCOS goes beyond theoretical importance; it presents potential therapeutic avenues. Supplementing with antioxidants to counteract OS has demonstrated potential in enhancing insulin sensitivity in PCOS patients.[33] Substances such as N-acetylcysteine[57], resveratrol[58], and α-lipoic acid[59] have been examined for their antioxidant capabilities and possible roles in altering insulin resistance associated with PCOS. Therefore, OS is instrumental in the onset and progression of insulin resistance in PCOS-afflicted women.[25] The multifaceted molecular mechanisms connecting OS to weakened insulin signaling highlight the intricate nature of this endocrine condition.[25, 26, 60] A thorough understanding of these pathways not only demystifies PCOS pathogenesis but also paves the way for tailored therapeutic approaches that target the foundational oxidative environment, offering a brighter outlook for patient outcomes.

Impact on inflammation and immune responses

Although the ovarian changes in PCOS are well-documented[34,47], it is essential to comprehend the complex interplay between PCOS, systemic inflammation, and immune responses. Delving into these relationships can provide a deeper understanding of the disease's pathophysiology and inform potential therapeutic strategies for PCOS.

Systemic Inflammation in PCOS

PCOS patients often exhibit a marked presence of chronic low-grade inflammation.[20] In these individuals, there is a consistent elevation of inflammatory markers like C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) compared to their age-equivalent peers. This upsurge in pro-inflammatory indicators highlights an encompassing inflammatory condition, potentially intensifying both metabolic and reproductive complications of the syndrome.[20] Multiple factors contribute to this inflammatory state. For instance, adipose tissue, especially in those with PCOS, can release pro-inflammatory cytokines. Additionally, the often-seen hyperinsulinemia in PCOS might boost the secretion of these inflammatory agents, thus promoting an inflammatory milieu.[24]

Immune Cell Dysregulations

PCOS is associated with distinct changes in the composition and functionality of immune cells. There are documented increases in the counts and activity of monocytes and macrophages. These cells are capable of producing a diverse set of cytokines, further promoting inflammation.[19] Intriguingly, macrophages in the ovarian tissues of PCOS patients seem to secrete elevated amounts of pro-inflammatory cytokines compared to their healthy counterparts, pointing to an inherent shift in immune cell behavior.[61] Natural Killer (NK) cells, key players in innate immunity, demonstrate amplified cytotoxic actions in PCOS. While the exact consequences of this escalation are still under scrutiny, it is theorized that they might contribute to the perturbed folliculogenesis and absence of ovulation commonly observed in the disorder.[61]

Impact of chronic Inflammation on Metabolic Aberrations

The enduring inflammatory condition in PCOS is linked with insulin resistance, a predominant metabolic disruption witnessed in numerous PCOS sufferers.[25] Certain pro-inflammatory cytokines, notably TNF-α and IL-6, can disrupt insulin-mediated pathways, culminating in diminished cellular glucose uptake and resulting in hyperinsulinemia.[20] This state not only worsens the metabolic outcomes but also heightens the androgenic tendencies typical of PCOS, attributed to augmented androgen synthesis in the ovaries and adrenal glands.[26]

Understanding the influence of inflammation and immune disturbances in PCOS can shape treatment modalities. Agents with anti-inflammatory properties, including inositols, omega-3 fatty acids, and metformin, have demonstrated efficacy in mitigating PCOS manifestations, likely by addressing the foundational inflammatory condition.[62] The potential of immunomodulatory treatments is also an exciting frontier for research and therapeutic exploration.[63, 64] Thus, the widespread inflammatory and altered immune reactions are central to the onset and evolution of PCOS. Beyond the ovarian structural and hormonal adjustments, recognizing these systemic shifts is imperative for a comprehensive approach to PCOS management.[20] By mitigating these imbalances, not only can the direct symptoms of PCOS be alleviated, but associated risks of other chronic ailments, like heart disorders and type 2 diabetes, can be minimized, enhancing the overall life quality of the affected individuals.[26]

Relationship between oxidative stress and hormonal imbalances in PCOS

PCOS is a complex endocrine condition distinguished by a series of manifestations such as menstrual disturbances, elevated androgen levels, and the presence of numerous ovarian cysts.[5] The nuanced relationship between OS and endocrine imbalances has garnered significant scientific attention recently, shedding light on the underlying mechanisms of PCOS and suggesting possible treatment modalities.[11]

Oxidative Stress and Androgen Overproduction

A defining feature of PCOS is hyperandrogenism, which often presents as increased circulating androgens like testosterone.[5] Studies indicate that elevated ROS production in the ovarian theca cells of PCOS patients can activate the enzymes responsible for androgen biosynthesis. Notably, ROS can stimulate the cytochrome P450c17 enzyme, a central catalyst in the transformation of progesterone precursors to androgens, leading to a surge in testosterone and associated androgens, thereby intensifying hyperandrogenism.[12, 48] Additionally, the heightened androgen levels characteristic of PCOS can in return amplify OS. Androgens can boost ROS production by enhancing the function of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, essential enzymes in ROS generation.[48]

Oxidative Stress and LH Secretion

Elevated levels of luteinizing hormone (LH) are often observed in PCOS sufferers. OS significantly influences the secretion dynamics of LH.[14] ROS can activate the anterior pituitary, prompting an upsurge in LH synthesis and release. This rise in LH subsequently spurs further androgen output in the ovaries, creating a reinforcing cycle of hormonal dysregulation.[14]

Oxidative Stress, Follicular Development, and Anovulation

Folliculogenesis, the development process of ovarian follicles, is orchestrated by a series of endocrine signals.[46] Any disturbances in this cascade can culminate in anovulation, a frequent occurrence in PCOS. Heightened ROS levels in the ovaries of PCOS patients can hinder follicular maturation by negatively affecting granulosa cell growth and promoting cell apoptosis. This cellular disruption can obstruct the standard folliculogenesis pathway, resulting in the emergence of multiple immature follicles, a defining trait of PCOS.[47] Additionally, ROS-induced damage to the oocytes can degrade their viability, further contributing to reproductive anomalies in PCOS.[26, 47]

The interplay between OS and endocrine disruptions in PCOS is multifaceted and interlinked. While OS accentuates typical PCOS hormonal disruptions, such as hyperandrogenism, increased LH levels, and folliculogenesis anomalies, these hormonal disturbances reciprocally intensify OS, forming a self-propagating cycle exacerbating the underlying mechanisms of the disease.[12, 14] Identifying this dynamic interrelation offers therapeutic opportunities. By addressing ROS sources or strengthening the antioxidant defenses, it may be feasible to alleviate some PCOS-associated hormonal disruptions.[33] Conversely, rectifying these hormonal imbalances could decrease OS, emphasizing the value of a holistic management strategy for PCOS that encompasses both oxidative and endocrine pathways.[25]

OXIDATIVE STRESS AND PCOS-RELATED COMPLICATIONS

Cardiovascular risks

In women with PCOS, beyond the gynecological and metabolic consequences like anovulation and insulin resistance, there is increasing data indicating a higher susceptibility to cardiovascular diseases (CVD).[25] OS is a central factor underpinning this amplified risk. The relationship between OS and amplified CVD risks in PCOS[8] can be elucidated through several mechanisms:

Endothelial Dysfunction: OS has the potential to impair the endothelium, which constitutes the inner lining of blood vessels.[8] Dysfunction of the endothelium is a recognized antecedent to atherosclerosis. This can eventually result in an array of cardiovascular disorders, inclusive of coronary artery disease.[65]

Inflammation: Augmented levels of ROS can instigate an inflammatory cytokine cascade. Persistent inflammation has a direct association with atherosclerotic advancement, further intensifying cardiovascular threats.[66]

Lipid Dysregulation: Dyslipidemia, typically manifested as increased low-density lipoprotein (LDL) and diminished high-density lipoprotein (HDL), is frequently observed in women diagnosed with PCOS.[55] OS can facilitate LDL oxidation, yielding oxidized LDL. This modified LDL is more prone to fostering atherogenic conditions and encourages fatty plaque deposition within arterial structures.[56]

Hypertension: OS can modify the renin-angiotensin system and factors derived from the endothelium responsible for vasomotion, leading to heightened vasoconstriction.[67] This is a contributory factor to the onset of hypertension, a primary determinant for CVD.[8]

Platelet Aggregation: A surge in ROS can trigger platelet activation, enhancing their propensity to aggregate. The clumping of platelets is pivotal in the genesis of thrombi, events central to conditions like myocardial infarction and cerebrovascular accidents.[68]

OS is a primary conduit for the cardiovascular implications observed in PCOS. Grasping its role is pivotal to formulate specialized strategies to diminish CVD-related threats in this demographic.[8, 25]

Metabolic syndrome and Type 2 diabetes

PCOS is a complex endocrine disorder marked by a variety of clinical signs, with metabolic imbalances being particularly pronounced.[17] OS is integral to the onset of these metabolic irregularities, which encompass metabolic syndrome and Type 2 diabetes mellitus (T2DM).[18]

Metabolic syndrome is defined by a set of metabolic deviations including central adiposity, dyslipidemia, hypertension, and insulin resistance.[69] The occurrence of metabolic syndrome is notably higher in women diagnosed with PCOS compared to their age-similar peers. This heightened vulnerability is partly ascribed to the pronounced OS detected in PCOS. Elevated concentrations of ROS in the ovarian milieu and throughout the systemic circulation can perturb standard metabolic pathways, leading to insulin resistance – a distinguishing feature of both metabolic syndrome and T2DM.[54, 70]

T2DM emerges due to advancing insulin resistance combined with the inability of pancreatic beta cells to respond with augmented insulin production. The connection between PCOS and T2DM is evident, as those with PCOS have a raised propensity to develop T2DM.[18] The reasons behind this escalated risk are diverse, but OS is a critical influencer. Increased ROS generation in PCOS intensifies the malfunction of pancreatic beta cells, undermining their insulin-producing response to glucose elevation, resulting in hyperglycemia and the subsequent onset of T2DM.[17]

It is significant to note that the elevated androgen levels observed in PCOS also intensify OS. Androgens can prompt excessive ROS generation, creating a self-propagating cycle wherein OS boosts androgen concentration and reciprocally.[12] This cycle not only maintains the PCOS phenotype but also expedites the progression of metabolic syndrome and T2DM. The role of OS in PCOS is crucial in magnifying metabolic imbalances. The combination of augmented ROS levels and hyperandrogenism in PCOS paves the way for the emergence of metabolic syndrome and T2DM, underscoring the need for holistic therapeutic interventions addressing OS and its resultant metabolic issues.[48]

Infertility and reproductive issues

PCOS represents a complex endocrine disorder commonly observed in women during their reproductive years.[11] A primary clinical consequence of PCOS is infertility, resulting from the combined effects of several underlying factors that impair

reproductive function.[71] Notably, OS stands out as a crucial factor that intensifies the reproductive abnormalities in PCOS.[6, 16, 72]

Studies have shown that the ovaries of individuals with PCOS exhibit increased generation of ROS.[67] Under normal conditions, ROS are counteracted by antioxidant defenses to ensure cellular equilibrium. Nonetheless, in PCOS, an apparent disruption occurs, either due to excessive ROS production or decreased antioxidant activity.[48] This ensuing OS adversely affects the ovarian cellular environment, inducing cellular harm, lipid oxidation, and protein alterations.[34]

The implications of OS on the reproductive aspects of PCOS are multifaceted.[6] Primarily, OS can directly hinder the progression and maturation of ovarian follicles. The presence of heightened ROS concentrations in the follicular fluid of PCOS patients correlates with diminished oocyte integrity.[56] Additionally, OS can impede the function of granulosa cells, pivotal for both follicular growth and steroid hormone production. Dysfunctional granulosa cells can consequently lead to anovulation, a characteristic symptom of infertility in PCOS. Furthermore, OS might influence steroid hormone biosynthesis pathways, potentially altering the production of essential reproductive hormones. Increased levels of OS can decrease the availability of steroid forerunners and obstruct enzyme activities critical for the production of hormones like estrogen and progesterone.[35, 73, 74] These hormonal disruptions can negatively affect not only follicle development but also the endometrial environment, accentuating the reproductive difficulties encountered by women with PCOS.[11]

Lastly, heightened OS within the ovarian environment could instigate the secretion of pro-inflammatory agents.[20] Persistent inflammation might exacerbate the deterioration of the ovarian setting, leading to the cyst-like features seen in polycystic ovaries and inhibiting consistent ovulation.[15] Thus, OS emerges as a pivotal factor in the reproductive anomalies associated with PCOS, as it can cause direct ovarian damage, modify steroid hormone synthesis, and induce inflammation. Therapeutic approaches in the future that focus on mitigating OS might offer potential solutions for the reproductive complications linked to this condition.[6]

Mental health concerns and quality of life

PCOS represents a complex endocrine anomaly defined by ovarian irregularities, increased androgen levels, and the presence of multiple ovarian cysts.[58] Beyond the biological consequences, PCOS significantly impacts psychosocial well-being, affecting both emotional health and overall life quality of those diagnosed. Accumulating data indicate a central role of OS in the pathogenesis of PCOS and its associated psychological disturbances.[75]

Elevated OS markers are consistently observed in PCOS patients.[10] This amplified oxidative condition not only contributes to the hormonal and metabolic imbalances typical of PCOS but also has implications for the central nervous system (CNS).[75] Neurological consequences of excessive OS are diverse. An overproduction of ROS can harm neural cells and upset the equilibrium of neurotransmitters, which may precipitate mood irregularities.[76] Research demonstrates that individuals diagnosed with PCOS exhibit a greater incidence of anxiety, depression, and related mood disorders compared to the broader populace.[76] The decline in neurotransmitter levels such as serotonin and dopamine, a result of OS, might be instrumental in these mood anomalies.[77] Additionally, the physical manifestations of PCOS like obesity, acne, excessive hair growth, and hair loss, intensified by the detrimental effects of OS, can lead to reduced self-worth, perceptions of body image, and a decline in overall life satisfaction.[5, 78, 79] This interaction between physical manifestations and emotional distress can establish a feedback loop wherein stress enhances OS, further intensifying both the physical and psychological symptoms of the syndrome.[9] Thus, OS serves as a key link connecting the physiological complications of PCOS with its psychological repercussions. A comprehensive approach to PCOS management should consider not only its metabolic and endocrine irregularities but also the ramifications of OS on mental health and general life quality.[80] Highlighting the significance of OS may pave the way for specific therapeutic strategies and preventive actions, enhancing the emotional health of PCOS patients.[75, 76]

THERAPEUTIC IMPLICATIONS

Antioxidant supplements and their efficacy in PCOS

In recent years, a multitude of clinical trials have probed the therapeutic potential of antioxidant supplements for PCOS. This article offers a succinct overview of the clinical data on antioxidant supplementation in PCOS.

Myo-inositol and D-chiro-inositol

These endogenous isomers are at the epicenter of PCOS scientific inquiries. They are pivotal in insulin signaling and glucose homeostasis. Clinical investigations reveal that concomitant administration of myo-inositol and D-chiro-inositol ameliorates both metabolic and reproductive disturbances in PCOS.[81] A randomized study illustrated that PCOS-afflicted females receiving a mixture of these isomers experienced enhancements in insulin sensitivity, endocrine profiles, and ovulatory consistency compared to their counterparts without this treatment.[81, 82]

N-acetylcysteine (NAC)

NAC, a progenitor of antioxidant glutathione, has been analyzed for its prospective advantages in PCOS.[57] A randomized study demonstrated that when synergized with clomiphene citrate, NAC augmented ovulation and conception rates among PCOS patients resistant to clomiphene citrate. Furthermore, an additional trial verified that NAC diminished serum concentrations of MDA, an OS marker, and heightened insulin sensitivity in PCOS women.[57]

Vitamin E and C

The synergistic effect of Vitamins E and C has been probed owing to their antioxidant attributes and prospective therapeutic impact on PCOS.[28] Randomized clinical data suggest that simultaneous intake of Vitamins E and C decreased serum androgens and augmented endometrial thickness in PCOS patients.[27] This amalgamation also manifested a favorable trajectory in diminishing OS markers, yet the evidence is still preliminary.

Coenzyme Q10 (CoQ10)

CoQ10, pivotal for mitochondrial electron transport, also displays antioxidant properties. Clinical evaluations suggest that CoQ10 supplementation may ameliorate metabolic indicators in

PCOS.[83] Research indicated that CoQ10 supplemented PCOS females manifested a significant decrement in serum LDL cholesterol, overall cholesterol, and enhanced glycemic metrics relative to a control group.[84]

Omega-3 Fatty Acids

Omega-3 fatty acids, renowned for their anti-inflammatory characteristics, are theorized to attenuate certain PCOS symptoms via their antioxidant capacities. A randomized study indicated that omega-3 fortification resulted in reductions in serum triglycerides, androgens, and LH to FSH ratios among PCOS patients.[85, 86]

Resveratrol

This polyphenolic compound, predominantly sourced from grapes and berries, has exhibited anti-androgenic and antioxidant capabilities.[58] Clinical evaluations of PCOS females supplemented with resveratrol displayed a decline in testosterone, DHEAS levels, and enhanced insulin responsiveness. The antioxidant potential of resveratrol was further evidenced by the downturn of OS markers.[58, 87]

Melatonin

Recognized as a circadian rhythm modulator, melatonin also demonstrates antioxidant capabilities.[88] Clinical data hint that melatonin might enhance oocyte viability and stabilize menstrual regularity in PCOS females, probably attributable to its antioxidant actions against OS in follicular fluid.[89]

Current clinical findings propose that antioxidant supplementation could play a role in mitigating metabolic and reproductive irregularities in PCOS.[89] Ranging from rectifying insulin insensitivity to adjusting endocrine disparities and bolstering ovulatory processes, antioxidants such as NAC, CoQ10, myo-inositol, and resveratrol present encouraging outcomes.[57, 82, 83, 87] Nonetheless, it is imperative to tread with prudence, as more extensive research is needed to elucidate optimal dosages, potential adverse effects, and enduring benefits. Furthermore, it is vital to recognize these supplements as potential supplementary measures rather than primary therapies, integrating them into a holistic PCOS therapeutic strategy.[48]

LIFESTYLE MODIFICATIONS AND DIETARY APPROACHES TO MITIGATE OXIDATIVE STRESS

Addressing OS through alterations in lifestyle and nutritional strategies holds potential in the control of PCOS and the reduction of its associated complications.

Lifestyle Alterations

Physical Activities: Consistent physical activity can induce antioxidant effects by amplifying the inherent antioxidant system and minimizing the formation of ROS. Activities such as aerobic workouts, resistance training, and flexibility routines have demonstrated favorable outcomes. Additionally, by enhancing insulin sensitivity and decreasing insulin concentrations, physical activity indirectly curtails the OS related to insulin resistance, prevalent in PCOS.[90,91]

Weight Management: A considerable proportion of individuals diagnosed with PCOS exhibit overweight or obesity.[92] Even modest weight reduction (5-10% of starting body weight) has demonstrated a decrease in oxidative indicators and an alleviation of PCOS manifestations.[90] This weight loss can elevate insulin sensitivity, diminish inflammation, and cut down androgen concentrations, which collectively result in reduced OS.[91, 93]

Stress Reduction: Prolonged stress augments cortisol concentrations, potentially worsening insulin resistance and initiating OS. Approaches like mindfulness practices, yoga, meditation, and cognitive behavioral therapy have shown their efficacy in curbing OS markers by adjusting the stress response.[94-97]

Nutritional Interventions

Antioxidant-rich foods: The incorporation of antioxidant-rich foods can negate the detrimental impacts of ROS. Examples of these include (a) Vitamins: Primarily vitamin C (sourced from citrus fruits, strawberries, and bell peppers)[27] and vitamin E (located in almonds, sunflower seeds, and spinach)[28], (b) Polyphenols: Predominantly in berries, dark chocolate, green tea, and red wine[58, 87], (c) Carotenoids: Typical sources include carrots, sweet potatoes, and deep green vegetables.[98]

Omega-3 Fatty Acids: Predominantly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), these acids exhibit anti-inflammatory and antioxidant qualities.[86] Regular intake of fatty fish such as salmon, mackerel, and sardines, or fish oil supplements, is recommended.[85]

Inositol: The isomers Myo-inositol and D-chiro-inositol offer potential in addressing insulin resistance in PCOS. They play a role in amplifying insulin communication, which can reduce OS. Inositol-rich foods encompass beans, grains, and nuts, but therapeutic doses often come from supplements.[81, 82]

Dietary Fiber: Consuming a fiber-rich diet fosters improved glycemic regulation, diminishes hyperinsulinemia, and indirectly reduces OS. Dietary fiber sources entail whole grains, legumes, fruits, and vegetables.[99, 100]

Zinc: As an essential mineral, zinc possesses antioxidant attributes and has a role in insulin processing. Foods such as pumpkin seeds, lentils, and lean meats are high in zinc content.[29]

Reduce Glycemic Load: Intake of low glycemic index foods can promote insulin sensitivity and decrease the OS initiated by glucose. Choices like whole grains, legumes, non-starchy vegetables, and fruits with reduced sugar content are beneficial.[17, 18]

Minimize Processed Food Consumption: Excessive intake of processed foods can increase ROS due to unhealthy fats, sugars, and chemical additives. Reducing their consumption can assist in managing OS.[101]

For effective OS control in PCOS, a comprehensive strategy encompassing both lifestyle and nutritional modifications is essential.[4, 58, 99] Customizing these interventions according to individual specifications can ensure better results. It remains imperative to adopt these changes with the counsel of healthcare experts, given the intricate and personalized nature of PCOS.

Pharmacological interventions targeting oxidative stress in PCOS

Metformin: Initially developed as an antidiabetic agent, metformin has displayed advantageous outcomes in females with PCOS.[102] At the cellular level, metformin augments insulin responsiveness, which is theorized to curtail the generation of ROS.[40] Additionally, it has been evidenced to elevate the levels of antioxidative enzymes,

like SOD, leading to a decline in OS. Clinical investigations have recorded enhanced hormonal and metabolic indicators in PCOS subjects undergoing metformin therapy, alongside a reduction in OS markers.[40, 63, 102]

Inositols: Both myo-inositol and D-chiro-inositol have been spotlighted in PCOS therapeutic research. These inherent compounds are known to ameliorate insulin insensitivity, a recognized precursor to OS in PCOS. Moreover, research suggests that inositols might directly counteract OS, potentially by curtailing ROS generation or amplifying antioxidant protective systems.[81, 82]

N-Acetylcysteine (NAC): NAC, an antecedent to the robust antioxidant glutathione, has been evaluated for its prospective utility in PCOS management. Introducing NAC has been correlated with enhanced insulin responsiveness and a decline in OS indicators. Clinical evaluations have emphasized its efficacy in augmenting ovulatory processes and diminishing hyperandrogenism, either as a standalone or in conjunction with other therapies like clomiphene citrate.[57, 103]

Statins: Beyond their quintessential role in cholesterol regulation, statins possess antioxidative capabilities, which have been studied in relation to PCOS.[104] Some research indicates that select statins might reduce OS indicators in PCOS-affected females. However, the enduring safety of statins in this group requires more conclusive validation.[104]

Coenzyme Q10 (CoQ10): A constituent of the electron transport system, CoQ10 also serves antioxidative functions. PCOS patients, when supplemented with CoQ10, displayed diminished ROS generation and heightened antioxidant capability.[84] Further, clinical assessments hint at potential advantages of CoQ10 supplementation in refining metabolic and hormonal states in PCOS-affected women.[83]

Berberine: Derived from specific plants, this organic compound has been scrutinized for its antioxidative and anti-inflammatory traits.[105] In PCOS settings, berberine has proven to boost insulin responsiveness and directly counteract OS. Clinical observations, such as enhanced menstrual consistency and ovulation frequencies, have been documented post-berberine intake.[106]

Vitamin D: Traditionally linked with skeletal health, antioxidative potential of vitamin D has been under investigation.[107] Certain research posits a connection between vitamin D scarcity and heightened OS in PCOS.[29] Hence, vitamin D supplementation might address both this insufficiency and the OS.[4]

Antioxidant supplements: Diverse antioxidant supplements, encompassing vitamin E[28], vitamin C[27], and selenium[30], have undergone evaluation in the PCOS context. Their innate capability to neutralize ROS renders them potential therapeutic options. While specific research indicates positive impacts on hormonal and metabolic indicators in PCOS, comprehensive clinical validation for their broad application is still pending.[48, 108]

Future Directions and Unanswered Questions

Potential new biomarkers for oxidative stress in PCOS

Progress in molecular studies has facilitated the discovery of new biomarkers for OS in PCOS. Notable markers encompass 8-hydroxy-2'-deoxyguanosine (8-OHdG), an indicator of DNA oxidative harm[40]; advanced oxidation protein products (AOPP)[38]and MDA[34], markers for protein and lipid oxidation respectively; and the ratio of reduced to oxidized glutathione (GSH/GSSG), which offers a perspective on the cellular redox balance. Evaluating the activities of antioxidant enzymes, namely SOD and catalase, further clarifies the OS landscape in individuals with PCOS.[33]

Emerging therapies and their impact on oxidative stress

Novel therapeutic interventions for PCOS appear effective in counteracting OS. Coenzyme Q10, an essential element of the mitochondrial electron transport mechanism, has displayed efficacy in mitigating oxidative injuries when introduced as a supplement.[83,84] In a similar vein, resveratrol, an organic polyphenolic substance, has shown promise in bolstering antioxidant mechanisms and decreasing OS markers in those afflicted with PCOS.[58, 87] Omega-3 fatty acid supplementation may adjust the inflammatory process and diminish lipid oxidation, thus curtailing OS.[85,86] Furthermore, N-acetylcysteine (NAC), historically recognized as a mucolytic substance, has been found effective in restoring intracellular GSH concentrations and amplifying antioxidant capacities.[57, 103]

Long-term implications of addressing oxidative stress in PCOS

Addressing the OS components in PCOS could yield significant long-term advantages. Mitigating oxidative impairment might lower the likelihood of PCOS-related conditions like cardiovascular disorders[25], type 2 diabetes[18,25], and endometrial malignancies.[109] Enhancing the redox equilibrium might also offer relief from reproductive issues such as anovulation and infertility. By emphasizing the management of OS, medical professionals can aim at the molecular foundations of PCOS, potentially resulting in better clinical results, diminished symptom intensity, and an elevated overall life quality for those affected.[6,76]

Conclusion

PCOS is a prevalent endocrine dysfunction observed in reproductive-aged females, manifesting through a spectrum of clinical features such as menstrual anomalies, elevated androgen levels, and impaired fertility. The causative factors of PCOS are diverse, yet recent attention has been drawn to the significance of OS in its pathogenesis. The relationship between OS and PCOS is primarily attributed to an imbalance between the production of ROS and the body's antioxidative defense capabilities. This imbalance not only facilitates an inflammatory environment but also leads to the endocrine disturbances typical of PCOS. Contemporary research highlights increased oxidative markers in PCOS-affected women in comparison to unaffected individuals. This OS further intensifies hormonal aberrations, particularly magnifying insulin resistance, a frequent coexisting condition with PCOS. This self-perpetuating loop not only accentuates the clinical symptoms of the syndrome but also heightens the susceptibility to concomitant disorders like cardiovascular ailments and type 2 diabetes. As we deepen our grasp of the connection between OS and PCOS, it signals potential avenues for innovative treatment modalities. Manipulating oxidative pathways may be a potential supplementary treatment, working in tandem with standard therapies, offering a comprehensive management strategy for PCOS. Interventions such as antioxidant supplements[110-114] and

lifestyle alterations focusing on curbing OS could be beneficial in alleviating PCOS symptoms. As research progresses in this domain, the potential for more effective treatment modalities for PCOS becomes apparent.

Conflict of Interest

The authors declare that none of them has any conflict of interest.

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