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Effect of Exercise and Nutrition on Oxidative Stress in Females with Polycystic Ovary Syndrome, a Current Status and Future Perspective in Narrative Review

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ABSTRACT

Women in their reproductive years are prone to the widespread endocrinological disorder known as Polycystic Ovarian Syndrome (PCOS). To provide in-depth insights into the factors contributing to hormonal imbalances, inflammation, and oxidative stress in women with PCOS. Additionally, it evaluates the impact of exercise and nutritional interventions on oxidative stress and overall metabolic health in PCOS women to improve their quality of life. This review analyzed existing literature and clinical evidence related to endocrine disturbances in PCOS, including hormonal changes such as elevated androgens, insulin resistance, inflammation, and oxidative stress. The effects of lifestyle interventions specifically physical exercise, dietary modifications, and supplementation on these metabolic and hormonal abnormalities were studied. Hormonal Imbalance: Women with PCOS show dysregulated production of Growth Hormone (GH), ghrelin, LEAP-2, Gonadotropin-Releasing Hormone (GnRH), insulin, LH/FSH ratio, androgens, and estrogens. Inflammation and Oxidative Stress: Hyperandrogenism and insulin resistance promote chronic inflammation and increased Reactive Oxygen Species (ROS), leading to oxidative stress, gut microbiome alterations, and metabolic dysfunction. PCOS is a multifactorial disorder influenced by hormonal imbalance, chronic inflammation, and oxidative stress. Lifestyle modifications, particularly tailored exercise regimens and nutritional strategies, play a critical role in mitigating these factors.

INTRODUCTION

A prevalent endocrinological condition that affects women in their reproductive years is polycystic ovarian syndrome, or PCOS. The World Health Organization (WHO) estimates that 8-13% of women in their reproductive years have PCOS. While about 70% of females are still undiagnosed in general. Specifically, in Pakistan, this has a very alarmingly high prevalence of 52% [1]. The key features of PCOS are hyperandrogenism, metabolic disorder, and polycystic ovaries causing chronic anovulation. The most common hormones altered in females with PCOS are androgen, estrogen, insulin, cortisol, gonadotropin-releasing hormone (GnRH), luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio, and Growth Hormone (GH). Consequently, this imbalance may enhance the likelihood of resistance to insulin and being overweight while directly affecting psychological health. Furthermore, increased prevalence of obesity, long-term cardiovascular diseases, infertility, and pregnancy complications have been observed. Some evidence suggests that females taking medicine for the condition have increased chances of osteoporosis and the likelihood of bone fracture [2]. There are many different criteria for diagnosing PCOS, but the most commonly used clinical diagnosis criteria are NIH and Rotterdam. According to the former, a patient can only be

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diagnosed if symptoms like hyperandrogenism, or when the ovarian size and morphology on ultrasonography reveal the presence of 12 or more follicles measuring 2–9 mm in diameter or an increased ovarian volume > 10 ml, or there must be a disordered menstrual history (oligo or anovulation) [3]. Whereas the former defines PCOS as a syndrome characterized by ovarian dysfunction. The hallmarks include polycystic ovarian morphology and hyperandrogenism, as well as clinical symptoms that may include obesity, irregular menstruation, and indicators of androgen excess. The main symptoms of hyperandrogenism are irregular menstruation, acne, and hirsutism, which is excessive growth of terminal hair in masculine pattern distribution in women [4]. It is worth noticing that around 75% of females suffer from ovulatory infertility. These females choose in Vitro Fertilization (IVF) for conception, which in turn increases the chances of developing ovarian hyperstimulation syndrome. Furthermore, it also increases the risk of miscarriages and gestational diabetes during pregnancy [5].

Although the increasing awareness of oxidative stress as a major contributor to the pathophysiology of PCOS, there is a large gap in the literature on standardized, evidence-based protocols of exercise and nutritional interventions, specifically aimed at reducing oxidative stress in the patients of PCOS. The main issue is that there is the lack of high-quality, randomized controlled trials with sufficient sample sizes that directly measure the oxidative stress biomarkers as the main outcomes of response to lifestyle interventions in PCOS women. This study aims to analyze existing literature and clinical evidence related to endocrine disturbances in PCOS, including hormonal changes such as elevated androgens, insulin resistance, inflammation, and oxidative stress.

Contributing Factor

Many earlier studies showed several contributing factors that can be characterized as internal and external for the PCOS occurrence. Internal factors include but are not limited to oxidative stress, inflammation, hyperandrogenism, obesity, and insulin resistance. Some of the external factors include food, stress, and environmental toxins [6]. The pathological imbalance of the hormones (mentioned earlier) increases the prevalence of osteoporosis. Therefore, there is little evidence that the medications used to treat PCOS raise the likelihood of bone fracture via disrupting hormones [6]. Additionally, research has shown that the gut microbiota is the main factor contributing to obesity., diabetes, and inflammation in PCOS. It has been reported in studies that poor diet and lifestyle cause gut dysbiosis, which ultimately leads to the activation of lipopolysaccharides. Consequently, it results in the inactivation of the immune system, hyperandrogenism, and insulin resistance [7].

Chronic Low-Grade Inflammation

It has been seen in earlier studies that females suffering from PCOS experience chronic low-grade inflammation. This inflammation usually shows itself as an increased level of inflammatory markers and AGEs among them. Neutrophils, macrophages, and lymphocytes are the main cells that secrete cytokines, which are small proteins that function as signaling molecules to regulate the immune system, including initiating and controlling inflammatory response. Dysregulation of cytokines is strong enough to cause low-grade inflammation and, ultimately, cell death. Likewise, an additional element is Reactive Oxygen Species (ROS), engaged in producing chronic low-grade inflammation and a subsequent rise in oxidative stress load. An imbalance between the generation of free radicals and anti-oxidant defense mechanisms is known as oxidative stress. Elevated levels of Reactive Oxygen Species (ROS) cause cellular damage including DNA, protein, and lipid, which subsequently causes increased oxidative stress and inflammation [8]. All of this puts PCOS-afflicted women at higher risk for cardiovascular illness and other pregnancy issues, such as infertility or miscarriages [9].

Oxidative Stress

Oxidative stress is a normal physiological process in a body because of an imbalance between oxidant free radicals and antioxidants. Oxidants are free radicals with an unstable single electron in the outer shell of an atom which are highly reactive. These oxidants achieve stability by stealing electrons from antioxidants. A condition known as oxidative stress occurs when the quantity of free radicals exceeds that of antioxidants. This oxidative stress causes cell damage or even cell death leading to various pathologies, chronic inflammation, and the aging process [10]. These free radicals can be divided into two main classes namely, both reactive oxygen and reactive nitrogen species. These free radicals play a significant role in metabolic derangements like diabetes mellitus, cardiovascular disease, and obesity. Biomarkers for assessing the antioxidants can be used for early diagnosis and treatment and as a preventive measure for metabolic disorders [11]. A strong immune response is essential for the recovery of inflammation in the body caused by the oxidants. Inflammation and oxidative stress often create a vicious cycle where one process fuels the other, leading to a cascade of cellular damage and ultimately, decreased health outcomes. In contemporary research, lifestyle modifications have been considered fundamental in addressing PCOS. They serve as the primary treatment for individuals with obesity. Key interventions include dietary changes and enhanced physical activity. These modifications are associated with the normalization of ovulation and menstrual cycles, thereby improving

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pregnancy outcomes in PCOS females. Researchers have shown that nearly 50% of PCOS patients experience enhancements in menstrual regularity and ovulation due to lifestyle changes. Furthermore, such modifications can lead to reductions in anxiety and enhancements in life quality, especially for obese women with PCOS [12]. According to another study, women with PCOS are more likely to suffer from eating disorders, including binge eating disorder and bulimia nervosa. Major characteristic symptoms of the eating disorder are associated with behavioral, cognitive, and emotional features. A person with PCOS who suffers from eating disorders is more likely to experience body dysmorphia, stress, anxiety, and depression, all of which have a negative impact on their quality of life [13]. The variety of eating disorders associated with PCOS, including atypical anorexia nervosa, require more research. Significant detrimental effects on the health and quality of life of people with PCOS may be avoided with early detection and appropriate treatment of an eating disorder.

Current Status and Future Perspective Regarding Treatment of PCOS

This paper examines a detailed review of the health status of women with PCOS. It is an endocrine and metabolic disorder that causes hormonal imbalance as mentioned earlier. It describes the affirmative actions needed to avert and/or reduce the risk associated.

Exercise

For women with PCOS, lifestyle change has been proposed as the first-line therapy in along with medical intervention [14]. An essential component of PCOS management is physical activity, which helps alleviate symptoms and lower the chance of long-term illnesses like type 2 diabetes and cardiovascular disease. Both continuous and intermittent aerobic training exercise regimens are recommended by the American College of Sports Medicine (ACSM). Numerous previous research used submaximal heart rate aerobic activities, adhering to the American College of Sports Medicine's (ACSM) approved guidelines [15]. Women of normal weight should exercise an average of 150 minutes per week at a moderate effort, 75 minutes per week at an intense frequency, or an equal quantity of both, according to worldwide PCOS guidelines. Obese or overweight women with PCOS are advised to engage in moderate-intensity activity for 250 minutes per week, intense exercise for 150 minutes per week, or a combination of both [14]. Additionally, research on the effects of exercise therapy on fertility has shown improvements in the regularity of cycles of menstruation and/or ovulation [16]. The significance of exercise further increases due to the significant risk for Cardiovascular Diseases (CVD) in these women [16]. Exercise also improves insulin sensitivity and lowers hyperinsulinemia, which is the fundamental mechanism by which it decreases CVD risk variables. Meanwhile, PCOS has been linked to a higher prevalence of mental health conditions in addition to cardio metabolic and reproductive issues. The psychological health of the sick population is enhanced by exercise. Given the extremely individualized nature of PCOS, it may not be possible to establish an ideal dose-response connection with exercise [15]. According to current recommendations, one should engage in physical activity for at least 150 minutes per week; however, the optimal exercise regimen may vary among individuals. Exercise regimens that are customized for each PCOS-afflicted female based on her particular traits and reactions, are essential for maximizing health benefits in coordination with clinician or healthcare professional prescription [17]. To lessen the consequences of PCOS, some non-pharmacological strategies should be used. This suggests that engaging in regular exercise is a valuable strategy for reducing some of the symptoms associated with PCOS [18, 19]. As stated by Covington *et al* [18]. Because skeletal muscles produce cytokines and other peptides called myokines, they are regarded as organs with an endocrine role. As stated by Moro *et al.*, and Aghaie *et al.*, through the regulation of guanylyl triphosphatase GTPases, perilipin 3 PLIN3, catecholamine, and the atrial natriuretic peptide, both found that prolonged aerobic exercise was sufficient to improve lipolysis activity, which is reduced in individuals suffering from PCOS [19, 20]. These physical exercise regimes could be acute or chronic with varying intensities (low, moderate, or high intensity) based on the patient's needs. Anaerobic or aerobic metabolic processes may also be involved [21, 22].

Oxidative Stress and Exercise Relationship in PCOS Patients

The generic phrase "oxidative stress" refers to a disproportion between the body's capacity to use antioxidants to protect itself from the damaging effects of free radicals and the generation of these radicals. Cell death and/or mutations in DNA result from the imbalance [23]. Disruptions to the cells' normal oxidation response and the production of peroxides and free radicals can have toxic effects that damage the cell. To evaluate this imbalance, oxidative and anti-oxidative stress markers can be tested in the patients for timely intervention through pharmacological as well as physical therapy/exercise regimes. Some of these markers are mentioned in the following table 1 [24].

Table 1: PCOS Patients' Oxidative Stress Indicators [25]

Indicators of the Degree of Oxidative Stress	Source	OS Concentrations in PCOS Patients Compared to Normal
Malondialdehyde (MDA)	Serum; RBCs	High
Nitric Oxide (NO)	Serum	High

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Advanced Glycosylated End Products (AGEs)	Serum	High
Xanthine Oxidase (XO)	Serum	High

Table 2 summarized the variations in oxidative stress indicators among PCOS patients compared to healthy individuals.

Table 2: PCOS Patients' Oxidative Stress Indicators [26]

Indicators of the Degree of Oxidative Stress	Source	OS Concentrations in PCOS Patients Compared to Normal
Superoxide Dismutase (SOD)	Serum, Erythrocyte, and Follicular Fluid	High/Low
Glutathione Peroxidase (GPx)	Serum	Low
Total Antioxidant Capacity (TAC)	Follicular Fluid; Serum	High/Low
Vitamin E	Serum	Low
Vitamin C	Serum	Low

Both patients and medical professionals benefit from exercise training, which is important in the treatment of PCOS. Enhancing glucose transport and metabolism through physical activity results in improved insulin sensitivity. Increased glucose transport and metabolism brought about by physical activity improve insulin sensitivity. Exercise intensity affects how much a variety of physical characteristics improve. PCOS-affected women's levels of androgen and insulin sensitivity can be improved by engaging in strenuous activity, such as weight training and vigorous aerobic exercise for at least 120 minutes each week. Chronic inflammation in PCOS women can lead to increase ROS level which can be reduced mindful exercise and Yoga [27]. Nonetheless, yoga-based relaxation methods have been associated with lower oxygen consumption and are useful in lowering PCOS metrics [28]. Yoga can help lower the likelihood of PCOS by promoting conception and regulating endocrine factors [28]. Notably, exercise alone may not be sufficient to address a gynecological problem associated with hormones. Via the Hypothalamic-Pituitary-Gonadal (HPG) pathway, the hypothalamus is in charge of producing androgen and ovarian hormones. Follicle-stimulating hormone and luteinizing hormone, two gonadotropins that are of particular importance in PCOS, are produced and released by GnRH. The HPG axis releases LH in response to irregular GnRH discharge from the hypothalamus to the pituitary. Both inflammation and oxidative stress are disruptive factors that elevate the LH-FSH ratio and cause hyperandrogenism. Hypothalamic pathologies in PCOS result in hormonal imbalance and consequent metabolic disturbances like insulin resistance. Studies suggest that physical exercise plays a significant role in improving insulin sensitivity. Furthermore, a usual androgenic rhythm with a lower concentration of LH is the outcome of this insulin sensitivity. According to research by Bonab and Parvaneh, aerobic exercise has an impact on adolescent females suffering from PCOS [21]. Aerobic conditioning for 12 weeks was found to have a beneficial effect on lipid profile and to raise testosterone and estrogen levels. Jedel and colleagues demonstrated that 16 weeks of aerobic exercise was beneficial in treating hyperandrogenism and oligo/amenorrhea [29]. Physical activity training is progressively employed in the treatment of PCOS. Examination shows that intense exercise significantly boosts cardiorespiratory fitness, body composition, and insulin sensitivity. Evidence suggests that engaging in at least 120 minutes of intense exercise weekly is vital for achieving favorable health results in female PCOS patients [30]. Exercise has been shown to have enormous positive impacts on insulin resistance, particularly in women with PCOS, according to certain research. Health outcomes can get better from vigorous exercise, especially insulin resistance, cardiovascular fitness, and body fat or adiposity. High-intensity exercises, especially resistance exercises, increase insulin sensitivity and improve hyperandrogenic measurements [31].

Diet

One of the main risks associated with the environment that can be changed for preventative measures and early treatment of non-communicable illnesses is diet. One thing observe in PCOS female is lack of knowledge and poor quality of diet. The major portion of diet is on carbohydrate that contribute to weight gain and further lead to complication like insulin resistance, metabolic abnormalities [32]. A diet with fewer calories with lower levels of Glycemic Index (GI) is associated with a significant improvement in insulin resistance, oxidative stress, and chronic inflammation. Herbs with antioxidant properties are of importance in reducing chronic inflammation, along with liver steatosis. These are the supplements (inositol, thiamine, coenzyme Q10, vitamin D, zinc, and selenium) suggested for reducing chronic inflammation and having antioxidant properties [31]. Good intake of vitamins, and minerals like calcium, vitamin D, and herbs with antioxidant property could improve healthy hormonal balance, regular ovulation, increased estrogen level and healthy uterine lining in PCOS women [33]. Increased weight gain is more common in PCOS women and is causative factor of insulin resistance resulting in metabolic abnormalities and reproductive issues. These issues are more common in obese PCOS women as compared to lean PCOS women. so that's means IR is major complication of PCOS women so first line of treatment is life style modification, dietary changes and physical exercises are recommended along with medical treatment. Evidence proved that weight loss, by 5–10%, can increased insulin and testosterone levels and improve menstrual hormones. Among all different nutritional plans, the MD and KD is recognized as a best dietary plan due to its characteristics, like consumption of

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omega-3 unsaturated fatty acid, fatty acids, and diminished consumption of animal-derived proteins that may lower many risk factors for metabolic disorders such as endothelial dysfunction, fatty acids alterations and IR [33]. Single diet could not benefit a woman with PCOS. It is observed that mediterrranean diet and KD diet have beneficial effect on PCOS women. Pharmacological intervention plays important role in regulating menstrual cycle and reducing hyperandrogenism symptoms [34]. Increased carbohydrate consumptions always major source of obesity and this leads to insulin resistance [32].

Treatment/Management

Treatment for PCOS is symptomatic. Evidence showed that the use of oral contraceptives along with metformin improves hyperandrogenism response in PCOS. Particularly females who are obese showed a remarkable change in BMI [4]. To manage irregular menstruation, oral contraceptives are the primary line of treatment for female PCOS patients. Hirsutism, acne, and Oral contraceptives indirectly reduce the androgen hormone because of its impact on both the pituitary and hypothalamus, which promotes negative feedback for LH. Estrogen (ethinylestradiol) and anti-androgens (Cyproterone Acetate (CPA), drospirenone, norgestimate, levonorgestrel ,and desogestrel) are found in most oral contraceptive preparations. Although the exact processes are not yet understood, prebiotic, probiotic, and symbiotic treatment appears to have positive benefits and enhance many biochemical findings in women with PCOS [35].

Vitamin D

All vitamins have some importance in metabolic activities. Above all, vitamin D is necessary to preserve bone homeostasis and calcium metabolism. It is available from dietary sources and mainly from sunlight. Some studies have proved that vitamin D has a positive effect on glycemic control by increasing insulin resistance. It was more effective with a daily low dose of vitamin D. Folic acid, commonly referred to as vitamin B-9, and possesses neuroprotective, cardiac, anticancer, and antioxidant qualities. Additionally, in women with PCOS, folic acid supplementation affects glycemic, inflammatory, and oxidative stress markers [9]. Guidelines for women with PCOS include a physical activity component. Increased levels of insulin sensitivity markers are improved with regular prolonged bouts of aerobic exercise conducted with heart rate and/or VO2max monitoring. While some data suggest that strength or resistance exercise improves many androgens, further studies are necessary to validate this. The influence of yoga on androgens and insulin sensitivity suggests more research. To find out how various types of exercise impact adipokines and anti-Mullerian hormone levels in females with PCOS, more research is also required [36]. Using supplements like vitamins, minerals, probiotics, and other dietary supplements may help with PCOS symptoms [37]. A diet high in protein, moderate in carbohydrates, and low in fat, together with an active lifestyle, may greatly reduce PCOS symptoms. Accordingly, a suggestion has been made that future research studies and clinical trials should incorporate various issues such as diet and eating patterns, changes in behavior, herbal and supplemental treatment, and other practices related to lifestyle to draw reliable conclusions [38].

Limitations and Future Recommendations

The inherent weaknesses of the narrative review design are that the design does not have a systematic method of search, quality evaluation of the included studies, and quantitative synthesis, which may introduce selection bias and compromise the reproducibility of drawn conclusions. The majority of primary studies, listed in this review, have small sample sizes (most of them contain less than 50 participants, divided into two or more groups), short intervention periods (most of them include less than 8-16 weeks), and insufficient follow-up periods to determine the long-term sustainability of oxidative stress reduction. Multicenter randomized controlled trials with adequate sample sizes with a long period of follow-up (more than 12 months) of large scale and multicentric nature are urgently required to provide definitive evidence on exercise and dietary interventions aimed at oxidative stress reduction in PCOS women with stratification by PCOS phenotype and a diverse ethnic population including South Asians.

CONCLUSIONS

Based on all the description mentioned in this article, the management of the PCOS depends on sign and symptoms of the disease. The exercise and nutrition has proved to be beneficial effects in the management of PCOS women. The insulin sensitivity improved with regular aerobic exercises with some relaxation techniques to neutralize the effect of ROS. While some data suggest that strength or resistance exercise improves androgens which also help to reduce oxidative stress. Using ketogenic and mediterranean diet along with supplements like vitamins, probiotics are helpful in the reduction of oxidative stress in PCOS women. Meanwhile, PCOS woman are advised to take diet high in protein, moderate in carbohydrates, and low in trans-fat, together with an active lifestyle to get rid of these symptoms.

Authors' Contribution

Conceptualization: MM
Methodology: MM
Formal analysis: MM, NB, SS
Writing and Drafting: MM, NB, SS, AS, RA
Review and Editing: MM, NB, SS, AS, RA

All authors approved the final manuscript and take responsibility for the integrity of the work

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Conflicts of Interest

All the authors declare no conflict of interest.

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