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Research progress on selenium and polycystic ovary syndrome: A review

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Abstract

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder in women of reproductive age, marked by irregular ovulation, high androgen levels, and polycystic ovaries. These symptoms are often accompanied by insulin resistance, oxidative stress, and chronic low-grade inflammation. However, the precise causes of PCOS are not well understood. Selenium, a vital trace element, is involved in the formation of antioxidant enzymes, such as glutathione peroxidases, which influence redox balance, insulin sensitivity, and reproductive endocrine function. Recent studies have extensively explored the link between selenium and PCOS. This review examines the potential mechanisms of selenium in the pathophysiology of PCOS. Furthermore, it explores the potential benefits of selenium supplementation in managing this condition. By examining existing research, this article aims to offer novel perspectives that may advance our understanding of the causes and treatment options for PCOS, ultimately paving the way for more effective clinical interventions.

Keywords: Polycystic ovary syndrome; Selenium; Reproductive endocrinology; Oxidative stress; Inflammatory response

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1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder impacting 5–10% of women of reproductive age, significantly affecting fertility, physical and mental health, and family well-being.[1] The condition arises from a complex interplay of genetic predispositions and environmental factors, including the availability of trace elements and exposure to pollutants. A central feature of PCOS is hyperandrogenemia, characterized by excessive androgen production by ovarian theca cells. This condition is primarily driven by increased luteinizing hormone secretion and compensatory hyperinsulinemia secondary to insulin resistance, which is observed in approximately 75% of individuals with PCOS.[2] Insulin resistance worsens hyperandrogenemia and increases the risk of type 2 diabetes and cardiovascular diseases.[3] Chronic low-grade inflammation is increasingly acknowledged as a key characteristic of PCOS, alongside metabolic and endocrine dysfunction. Elevated inflammatory markers in the circulatory system indicate an inflammatory milieu that may be intricately linked to the pathogenesis and progression of the syndrome.[4-6]

Current therapeutic strategies for PCOS primarily focus on symptomatic management and personalized interventions. These encompass a range of pharmacological treatments, including hormones, medications, supplements, and herbal remedies, alongside non-pharmacological strategies such as dietary modifications, lifestyle alterations, and alternative therapies such as acupuncture and moxibustion.[7] However, the prolonged use of pharmacological agents can often lead to gastrointestinal discomfort, including nausea and diarrhea, as well as issues related to drug resistance. In light of these challenges, further research is urgently needed to screen and investigate additional pharmacological agents that may offer more effective and sustainable treatment options for women with PCOS. Through comprehensive and mechanistic studies, we can gain deeper insights into the syndrome's underlying mechanisms and develop more targeted and personalized therapies to address the complex needs of those affected by PCOS.

Recent academic studies have focused extensively on the relationship between trace elements and PCOS, suggesting that these elements may impact metabolic processes, hormonal balance, and inflammatory responses, potentially contributing to the development of PCOS.[8] Selenium is a vital trace element necessary for normal physiological functions. It is renowned for its antioxidant and anti-inflammatory properties, as well as its ability to enhance reproductive health. Earlier studies have already demonstrated selenium's benefits in restoring ovarian function and mitigating pregnancy-related complications in women with PCOS.[9] Recent studies indicate that daily supplementation of 200 μg of selenium for 8–12 weeks can reduce insulin resistance, inflammation, and oxidative stress in women with PCOS.[10] These findings underscore the importance of further exploring the mechanisms through which selenium interacts with PCOS, as understanding its role in the pathophysiology of the condition could lead to the identification of novel targets for prevention and treatment.

2. Methodology

We performed an extensive literature review in PubMed and Cochrane Library using the English keywords "polycystic ovary syndrome," "PCOS," "selenium," and "ferroptosis." In addition, we performed a search for the Chinese keywords "多囊卵巢综合征 (polycystic ovary syndrome)、硒 (selenium)、铁死亡 (ferroptosis)" within the China National Knowledge Infrastructure database.

The inclusion criteria were as follows: (i) the research content must be closely associated with PCOS and selenium; and (ii) the literature must exhibit a high quality of evidence in comparable studies. The exclusion criteria were as follows: (i) non-English and non-Chinese publications; and (ii) theses and conference papers.

The process of literature screening involved independent evaluation and cross-verification by two individuals, following these specific steps:

(i) Deduplication: All literature exported from the database was imported into EndNote 21 (Clarivate, United States), a literature management software. The software's deduplication function was employed to remove duplicate entries across databases, with two researchers manually verifying the deduplication results to identify and eliminate any remaining duplicates.
(ii) Initial screening: Two researchers independently reviewed the titles and abstracts of the deduplicated literature. They initially evaluated the literature's relevance using predefined inclusion and exclusion criteria to identify studies that met the requirements.
(iii) Rescreening: For literature that passed the initial screening, full texts were obtained. Two researchers thoroughly reviewed the content and rigorously screened it according to inclusion and exclusion criteria to finalize the literature selection.
(iv) Dispute resolution: In the event of differing opinions between the two researchers during the screening process, initial attempts at resolution involved negotiation and discussion. If these efforts were unsuccessful, a third senior researcher was invited to participate in the evaluation. The final screening results were determined through a voting process.

Ultimately, 67 articles were included based on the established inclusion and exclusion criteria (Figure 1).

3. Physiological functions and metabolic characteristics of selenium

3.1. Physiological functions of selenium

Selenium is a crucial trace element necessary for maintaining optimal human health.[11] It plays several vital roles in biological functions, including exhibiting antioxidative and anticancer activities, supporting the immune system, protecting cardiovascular health, enhancing reproductive capabilities, lowering blood glucose levels, and regulating intestinal microbiota.[12] Selenium primarily exists in the body as selenoproteins, which are vital for various physiological and metabolic processes. Among these selenoproteins, glutathione peroxidases (GPXs) are among the best-characterized selenoproteins and are central to antioxidant defense. These selenoproteins contain selenocysteine residues at their active sites, playing a critical protective role against oxidative stress.[11]

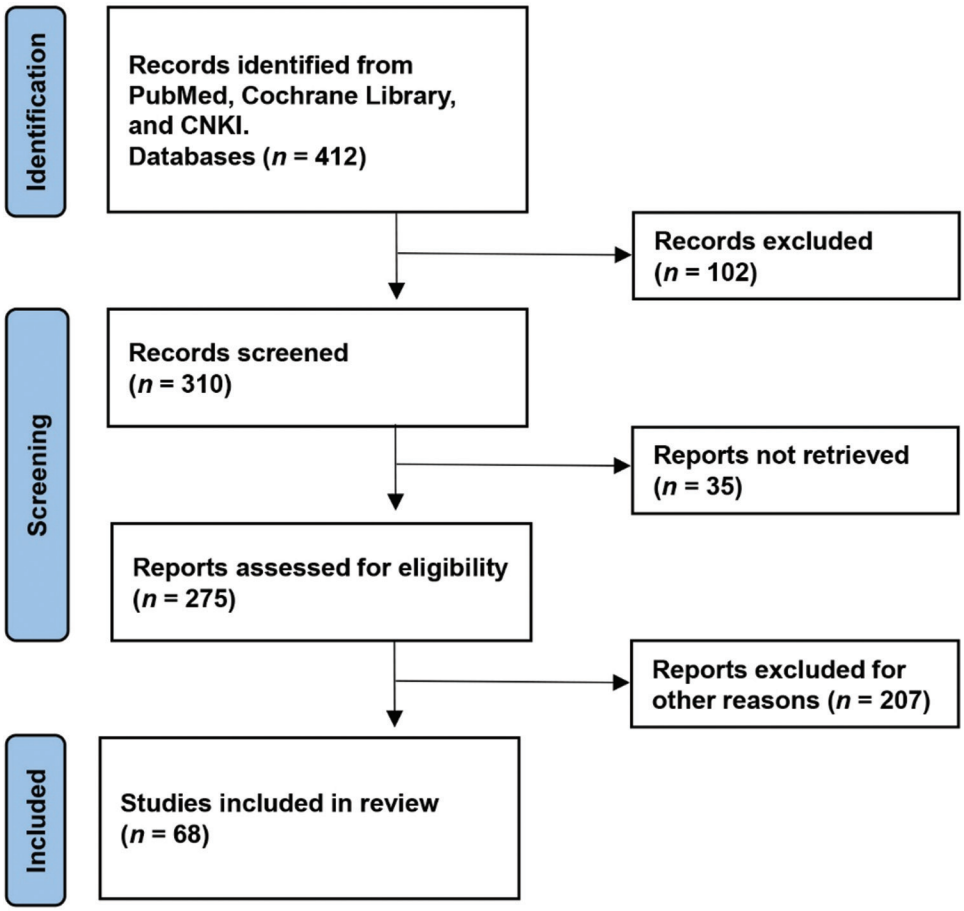

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study

3.2. Metabolic characteristics of selenium

Selenium absorbed in the intestine following ingestion primarily reaches the liver through the bloodstream for metabolic processing. These metabolites are then circulated throughout the body tissues, where they undergo further transformation and utilization. Selenium is essential in metabolic pathways, where it integrates selenocysteine into proteins to form selenoproteins, which perform antioxidant functions.

Disruptions in selenium metabolism can lead to various diseases. Selenium deficiency is associated with an increased risk of degenerative joint disease and Kawasaki disease, while selenium supplementation can help reduce the incidence of these conditions.[13] It is essential to note that different selenium forms exhibit distinct metabolic pathways and varying bioavailability within the body. Organic selenium compounds, such as selenomethionine, offer improved bioavailability and reduced toxicity compared to inorganic selenium forms (Figure 2).[14]

4. Pathophysiological mechanism of selenium in preventing PCOS

4.1. Selenium improves PCOS by inhibiting oxidative stress

Oxidative stress arises from an imbalance between pro-oxidant processes and antioxidant defenses, resulting in either excessive production of reactive oxygen species (ROS) or insufficient antioxidant clearance, ultimately leading to cellular damage. Research suggests that oxidative stress plays a crucial role in the development of PCOS. Patients with PCOS typically exhibit elevated oxidative stress, indicated by higher malondialdehyde (MDA) levels and reduced activity of antioxidant enzymes such as superoxide dismutase (SOD) and GPXs.[15,16] Oxidative stress impairs ovarian function, reducing oocyte quality and increasing the risk of infertility.[17] In addition, PCOS patients frequently exhibit low-grade chronic inflammation, which is closely linked to the inflammatory response triggered by oxidative stress. This inflammation exacerbates metabolic disorders and insulin resistance through mechanisms involving oxidative stress.[18]

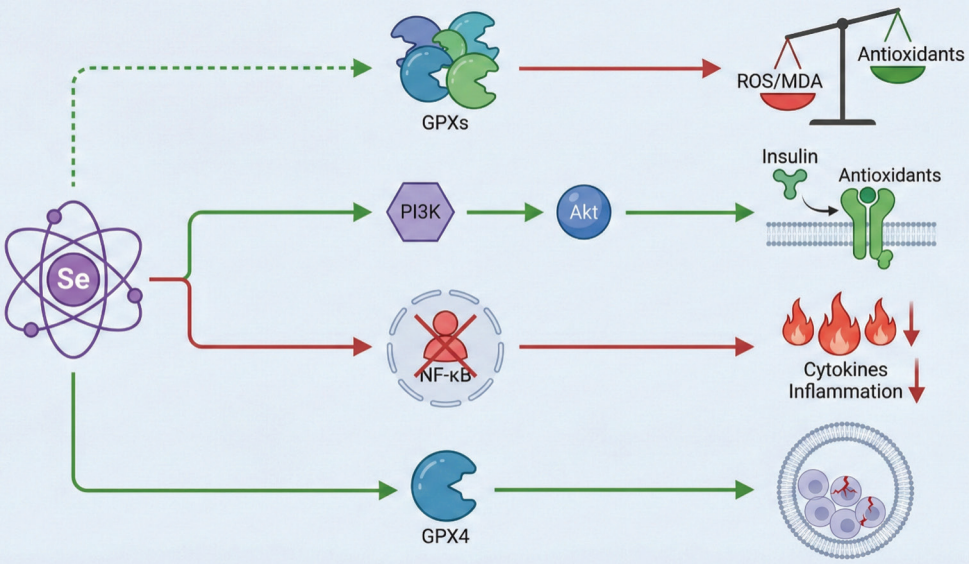

Figure 2. Potential mechanisms by which selenium affects PCOS. Image created by the authors using Google Gemini 3 Pro.
Abbreviations: GPX: Glutathione peroxidase; MDA: Malondialdehyde; NF-κB: Nuclear factor kappa B; PCOS: Polycystic ovary syndrome; PI3K: Phosphoinositide 3-kinase; ROS: Reactive oxygen species.

Given these findings, therapies aimed at reducing oxidative stress are being explored as potentially effective strategies to ameliorate PCOS symptoms. Numerous studies have focused on the use of antioxidants to mitigate the effects of oxidative stress in patients with PCOS.[19] In this context, selenoproteins, which are essential antioxidant proteins, play a significant role. Selenium supplementation enhances the activity of antioxidant enzymes, such as GPXs, SOD, and catalase (CAT), in multiple tissues (e.g., liver and breast) and in circulation, reflecting a systemic boost in antioxidant capacity.[20] A study on 40 infertile women with PCOS undergoing *in vitro* fertilization revealed that 8 weeks of organic selenium supplementation significantly reduced MDA levels.[21] This finding reinforces the potential of selenium supplementation to mitigate oxidative stress-related cellular damage, suggesting its therapeutic value for patients with PCOS. However, the study's small sample size limits the statistical power of the analysis, making it difficult to rule out random errors as a potential influence on the results. Consequently, further large-scale studies are necessary to substantiate these findings.

The antioxidant properties of selenoproteins are primarily attributed to the strong reducing capabilities of their selenocysteine residues. Selenium is crucial for boosting cellular antioxidant capacity by regulating intracellular defense mechanisms and enhancing glutathione synthesis. Selenium's importance in maintaining redox homeostasis is evident through its involvement in the Kelch-like ECH-associated protein 1 (KEAP1)–nuclear factor erythroid 2-related factor 2 (NRF2) signaling pathway, a crucial regulator of cellular antioxidant responses. Studies have demonstrated that selenium-enriched peptides can interact with KEAP1, stabilize NRF2, and upregulate the expression of antioxidant enzymes, effectively lowering ROS levels and protecting cells from oxidative damage.[22] Selenium exerts its antioxidant effects not only by directly scavenging ROS but also by modulating mitochondrial energy metabolism and biosynthesis, thereby enhancing cellular energy metabolism and mitigating oxidative damage at the molecular level.[23] Animal studies have indicated that selenium nanoparticles effectively decrease MDA levels and enhance SOD and CAT activities in the ovaries, muscles, and liver of rats with PCOS.[24] These findings suggest that selenium nanoparticles possess powerful antioxidant properties and may help ameliorate oxidative stress associated with PCOS.

4.2. Selenium enhances insulin sensitivity in PCOS by modulating the insulin signaling pathway

Insulin resistance is a central feature of PCOS, with selenium playing a crucial role in modulating insulin signaling, particularly through the phosphoinositide 3-kinase (PI3K)/serine/threonine kinase (Akt) pathway. Research has shown that selenium improves insulin resistance by influencing key components of the PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway. Selenium mitigates excessive ROS through the GPX family, thereby preventing oxidative damage to essential kinases, such as PI3K and Akt, and preserving the integrity of the pathway. Physiological ROS levels act as secondary messengers, promoting insulin receptor substrate phosphorylation,

which activates the PI3K/Akt/mTOR pathway to enhance glucose transport and glycogen synthesis.[25,26] In research involving animal models, the administration of selenium-enriched green tea polysaccharides to insulin-resistant mice significantly improved their insulin sensitivity.[27] This intervention resulted in decreased blood glucose and insulin levels, improved liver health, and reduced oxidative stress damage. A study of 70 pregnant women with gestational diabetes revealed that 6 weeks of selenium supplementation significantly reduced fasting blood glucose levels, serum insulin levels, and the insulin resistance index.[28] Notably, the insulin sensitivity check index was improved, suggesting selenium supplementation may benefit patients with gestational diabetes. Some studies indicate that selenium supplementation could worsen insulin resistance in individuals with PCOS over a 12-week period.[29] This variation may be attributed to several factors, including the baseline health status of the study participants, the dosage and timing of selenium supplementation, and individual differences in selenium metabolism. The baseline health status of the participants is a critical determinant. Responses to selenium can vary significantly among healthy individuals, those with metabolic abnormalities due to selenium deficiency, and those with comorbidities. In addition, age can influence the effects of selenium by altering metabolic function. The effects of selenium supplementation are significantly influenced by its dosage and timing. Individual differences in selenium metabolism, such as genetic polymorphisms, along with variations in lifestyle and dietary nutritional backgrounds, can further impact the absorption, utilization, and function of selenium. Furthermore, variations in the forms of selenium and the heterogeneity of research designs may exacerbate these differences in impact to some extent.

Although studies suggest that higher selenium levels may reduce insulin resistance, definitive evidence linking selenium levels to the risk of PCOS is lacking.[30,31] In summary, there is a pressing need for extensive, high-caliber research to elucidate the impact of selenium on insulin resistance. This is crucial for diverse populations and various selenium supplementation protocols to enhance our understanding of how selenium may mitigate insulin resistance mechanisms.

4.3. Selenium slows down the progression of PCOS by inhibiting chronic inflammation

Chronic inflammation plays a pivotal role in the progression of PCOS.[32] Studies have shown that women diagnosed with PCOS have a significantly higher count of inflammatory cells in their bloodstream compared to those without the condition.[33] This continual inflammatory reaction can lead to immune system dysregulation, impacting various bodily systems, including the reproductive, cardiovascular, digestive, and endocrine systems, which are associated with PCOS.[34] Selenium, a trace mineral, has been identified for its essential function in regulating inflammatory responses.[35] In a research study conducted by Jamilian *et al.*,[36] 60 PCOS patients were given a combination of probiotics and selenium supplements for 12 weeks. The findings demonstrated a significant reduction in high-sensitivity C-reactive protein levels, an increase in total antioxidant capacity (TAC), elevated total glutathione levels, and decreased MDA levels. The results suggest that selenium significantly reduces inflammation and oxidative stress in individuals with PCOS. A study by Butt *et al.*[24] showed that a 2-week administration of selenium nanoparticles at 25 ppm daily significantly reduced the expression of inflammatory cytokines, including interleukin-6, tumor necrosis factor-alpha (TNF-α), and interleukin-1, in a rat model of PCOS. Selenium reduces inflammation by inhibiting the activation of inflammatory signaling pathways, such as the nuclear factor-kappa B, which, in turn, decreases cytokine expression. Selenium's antioxidant properties help decrease ROS production, mitigating oxidative stress-induced cellular damage and indirectly reducing inflammatory responses.

The chronic inflammation in PCOS is closely associated with dysregulated lipid metabolism, forming a vicious cycle that exacerbates disease progression. Chronic inflammation has the potential to disrupt signaling pathways related to lipid metabolism, thereby exacerbating lipid disorders and abnormalities in lipid composition. This consequently triggers oxidative stress, promoting sustained inflammatory responses. The resultant cascade of inflammation, lipid disorder, and oxidative stress closely aligns with the core characteristic of iron-dependent lipid peroxidation. Selenium's anti-inflammatory and antioxidant properties can disrupt the cycle of lipid peroxidation observed in patients with PCOS. Exploring selenium's ability to improve lipid metabolism disorders and the pathological conditions of PCOS through ferroptosis modulation offers a promising avenue for future research.

4.4. Selenium improves the lipid peroxidation status of PCOS by inhibiting ferroptosis of ovarian cells

4.4.1. A state of lipid peroxidation in PCOS

Patients with PCOS often face challenges with lipid metabolism, as shown in various research studies. Dyslipidemia, marked by elevated triglycerides (TGs) and altered low-density lipoprotein cholesterol, is prevalent in individuals with PCOS. In addition, these

patients often exhibit reduced antioxidant and anti-inflammatory capabilities in high-density lipoprotein (HDL), along with an elevated HDL inflammatory index. These lipid abnormalities are closely linked to insulin resistance, increased oxidative stress, hyperandrogenism, and irregular HDL composition in PCOS patients.[37,38] A study of 106 PCOS patients found that approximately 45.7% exhibited dyslipidemia, mainly characterized by reduced HDL cholesterol (HDL-C) levels. Central obesity, hypertriglyceridemia, elevated abdominal blood glucose, and hypertension were also prevalent among these individuals.[39] Research has indicated that PCOS patients with metabolic syndrome have higher total cholesterol and TG levels, lower HDL-C, elevated TNF-α, and reduced granulocyte colony-stimulating factor in their follicular fluid.[40] Notably, granulocyte colony-stimulating factor exhibits a negative association with TG and total cholesterol, whereas TNF-α is positively correlated with TG, which may impact the quality of embryos and potentially affect embryonic development. Although lipid metabolism issues are common in PCOS patients, the exact causal relationship between these abnormalities and PCOS remains uncertain. Additional factors, such as obesity and insulin resistance, may also influence this association. Further investigation is required to clarify the complex relationship between lipid metabolism abnormalities and PCOS, highlighting potential treatment and management strategies for those affected.[41]

4.4.2. The connection between ferroptosis and lipid peroxidation

Ferroptosis is a unique form of programmed cell death triggered by iron, distinct from apoptosis and necrosis. This process is primarily driven by iron-dependent lipid peroxidation, marked by iron level imbalances, lipid oxidative damage, and reduced antioxidant activity.[42] Specifically, ferroptosis can be driven by the accumulation of free divalent iron in cells, initiating lipid peroxidation through the Fenton reaction with unsaturated fatty acids. Researchers have proposed that mitochondria or nicotinamide adenine dinucleotide phosphate oxidase may contribute to lipid peroxidation by producing ROS alongside iron metabolism.[43] As a result, lipids are continuously oxidized, leading to the buildup of harmful lipid peroxides that overwhelm the cell's antioxidant defenses, particularly GPX4. Excessive lipid oxidation compromises cell membrane integrity, ultimately leading to cell death.[44] A delicate balance exists between lipid peroxidation and antioxidants in regulating ferroptosis. Activating GPX4 inhibits lipid peroxidation and prevents cell death, whereas increasing lipid peroxidation induces ferroptosis. This bidirectional relationship between the two processes underscores the importance of maintaining iron homeostasis and antioxidant defenses to prevent cell death through ferroptosis.

4.4.3. Ferroptosis inhibition by selenium

Recent research has shed light on the critical role of selenium in preventing ferroptosis by influencing the activity of the essential antioxidant enzyme GPX4.[45] As a central inhibitor of ferroptosis, GPX4 protects cells from ferroptotic damage under various conditions.[46] Under typical physiological conditions, GPX4 uses glutathione to transform harmful lipid hydroperoxides into harmless lipid alcohols, effectively halting lipid peroxidation and preventing the onset of ferroptosis.[47] Moreover, studies have indicated that reducing endoplasmic reticulum stress can significantly decrease the likelihood of ferroptosis in colonic epithelial cells.[48,49] Selenoprotein K, located in the endoplasmic reticulum, is crucial for preserving the organelle's equilibrium. Excessive mechanical stress can trigger endoplasmic reticulum stress, leading to calcium overload and ultimately inducing ferroptosis. However, experiments involving nucleus pulposus cells exposed to mechanical overload, supplemented with selenomethionine, revealed promising results.[50] The addition of selenomethionine resulted in increased selenoprotein K expression, reduced endoplasmic reticulum stress, lower levels of intracellular calcium ions, and improved regulation of the extracellular matrix. This alleviation of stress disrupts the harmful feedback loop between endoplasmic reticulum stress and ferroptosis, effectively preventing the occurrence of ferroptosis. In addition, selenium enhances the activity of GPX4 and selenoprotein K, thereby improving cellular function and reducing susceptibility to ferroptosis. By increasing the expression of various selenoproteins, selenium can collaboratively combat ROS, mitigate ROS-induced damage, and shield cells from oxidative stress, ultimately safeguarding against ferroptosis. Overall, selenium emerges as a promising agent in the battle against ferroptosis, offering a multi-faceted approach to cellular protection and health.

Selenium effectively addresses the complexities of PCOS due to its anti-inflammatory and antioxidant properties. It helps to reduce chronic inflammation, improve insulin sensitivity, and regulate hormone production, all of which are key factors in treating PCOS. Considering the complexity of PCOS-related inflammation, selenium supplementation is expected to become a promising adjunctive therapy strategy in addition to conventional treatment. Further investigation is required to establish the optimal dosage and long-term safety of selenium supplementation. Further clinical trials are required to comprehensively assess its potential in treating PCOS.[19]

5. Evaluation of selenium concentrations in PCOS patients and their clinical implications

5.1. Analysis of the correlation between selenium levels and PCOS

Genetic predispositions, dietary practices, and environmental variations contribute to the diverse associations observed between selenium levels and PCOS across different ethnic groups. In some populations, selenium concentrations may correlate more strongly with androgen levels in individuals with PCOS, while this association might not be observed in other groups. Age may influence the relationship between selenium levels and PCOS. Selenium requirements may vary for women during puberty and childbearing years, potentially influencing the association between selenium levels and PCOS. However, current research on this topic remains limited, necessitating further comprehensive investigation.[51] Despite individual variability in selenium levels across populations, statistical analyses of PCOS across difference body-composition groups indicate that obese PCOS patients are more likely to experience selenium deficiency, as evidenced by reduced serum selenium levels. Research indicates a negative correlation between serum selenium levels and insulin resistance, implying that selenium deficiency may play a significant role in the progression of obesity-related PCOS.[52]

5.2. The role of selenium level detection in the diagnosis of PCOS

Recent research has pointed toward the importance of selenium level detection in diagnosing PCOS. An analysis of 264 PCOS patients and 151 controls revealed significantly lower serum selenium levels in individuals with PCOS compared to controls.[53] Another study focused on 125 PCOS patients aged 18–25, assessing various markers, including thiobarbituric acid reactive substances, TAC, SOD, GPX, and CAT activity, as well as levels of selenium and selenoprotein P.[54] The findings demonstrated that selenoprotein P levels were inversely related to thiobarbituric acid reactive substances and positively associated with TAC levels and erythrocyte GPX activity. This indicates a potential link between selenium levels and the development of PCOS. Some studies have reported no significant differences in selenium levels between individuals with PCOS and those without.[55]

Although studies on the link between selenium levels and PCOS diagnosis are scarce, incorporating blood selenium levels as a diagnostic reference in clinical settings may enhance the diagnosis of PCOS. In conjunction with hormone levels and ultrasound examinations, monitoring selenium levels may provide valuable information for developing personalized treatment plans. By examining selenium levels, healthcare providers can gain insights into a patient's antioxidant capacity, which is crucial for understanding the metabolic and oxidative stress status of individuals with PCOS. This approach could help in evaluating the severity and progression of the disease, ultimately leading to more effective interventions.[21] However, further research is necessary to determine the optimal threshold and clinical significance of selenium level detection in the diagnosis of PCOS. This integrated approach holds promise for enhancing the management and care of individuals affected by PCOS.

5.3. The role of selenium biomarkers in the diagnosis of PCOS

Identifying selenium-related biomarkers is essential for understanding and diagnosing PCOS. Current research shows that biomarkers such as GPX3 and selenoprotein P are dysregulated in PCOS patients, with decreased levels observed in both follicular fluid and serum. These biomarkers play a role in follicular development and reproductive outcomes in individuals with PCOS. Research has found a link between selenium levels in follicular fluid, GPX3 activity, and oocyte quality in women undergoing assisted reproductive technology.[56] This suggests that selenium may impact follicular development through these biomarkers. Therefore, examining selenium-related biomarkers may offer crucial insights into PCOS pathogenesis and diagnosis, enhancing management and treatment strategies for affected individuals.

6. Selenium supplementation therapy for PCOS

6.1. Impact of selenium supplementation on reproductive endocrinology and ovarian function

Research has increasingly indicated that selenium deficiency significantly affects ovarian function and fertility. When the body lacks selenium, its antioxidant defense mechanisms may be compromised, leading to issues such as impaired ovarian function, decreased oocyte production, and reduced fertility.[57] This deficiency is associated with adverse pregnancy outcomes, such as miscarriage, preeclampsia, and fetal growth restriction. Research indicates that selenium supplementation may be beneficial in managing PCOS.[58] A 3-month supplementation regimen with trace elements, including folate, selenium, Vitamin E, catechins, glycyrrhizin, and coenzyme Q10, resulted in reduced levels of anti-Müllerian hormone, total testosterone, luteinizing hormone, follicle-stimulating hormone, and the luteinizing hormone/

follicle-stimulating hormone ratio in patients with PCOS.[59] This suggests that selenium may benefit women with this condition. In addition, research indicates that selenium can improve TAC and enhance follicle quality in certain PCOS patients experiencing oxidative stress.[9] A study on 64 women with PCOS found that taking 200 μg/day of selenium for 8 weeks significantly increased pregnancy rates compared to a placebo.[15] This supplementation also resulted in reduced serum dehydroepiandrosterone levels and improvements in symptoms such as hirsutism and acne. Furthermore, studies on PCOS-induced rats have shown that oral administration of nano selenium at varying concentrations can restore their estrous cycle, lower body mass index, reduce insulin resistance, decrease serum testosterone levels, improve blood lipid profiles, and enhance ovarian histopathological features.[60] Overall, the research suggests that selenium deficiency can have negative implications for ovarian health and fertility, and its supplementation may offer therapeutic benefits, particularly for women with PCOS.

6.2. Integration of selenium into the standard treatment of PCOS

The combination of selenium with traditional treatments for PCOS could have a powerful impact. Common approaches to managing PCOS involve lifestyle adjustments and medications such as metformin and oral contraceptives. A study by Rabah *et al.*[61] demonstrated that the combination of selenium and metformin significantly enhanced insulin sensitivity, lipid metabolism, sex hormone levels, and ovarian health in a rat model of insulin-resistant PCOS. This combination outperformed metformin alone in enhancing the overall condition of the rats. The study revealed that the dual therapy effectively regulated the PI3K/Akt signaling pathway and enhanced anti-inflammatory and antioxidant functions. By integrating selenium with conventional treatments, there may be a holistic approach for managing PCOS, offering potential benefits beyond individual therapies.

Combining selenium with other medications or supplements can provide significant benefits. A 12-week course of probiotics and selenium has been shown to enhance psychological well-being and hormonal balance, while also reducing inflammation and oxidative stress in PCOS patients.[36] This integrated approach offers new insights into treating PCOS by targeting multiple mechanisms. Additional studies are required to identify the optimal combination therapies for enhancing treatment outcomes. This suggests that selenium, when used in combination with other treatments, has the potential to effectively manage the symptoms of PCOS. It highlights the importance of exploring innovative approaches to enhance the quality of care for individuals with this condition.

6.3. Safety and dosage selection of selenium supplementation

The safety of selenium supplementation for managing PCOS remains a debated topic. Various research studies have indicated that moderate selenium intake, such as 200 μg/day, is generally well-tolerated among different populations. Daily supplementation of 200 μg of selenium in individuals with human immunodeficiency virus has been associated with a slower decline in cluster of differentiation 4 cell counts and minimal adverse effects.[62] Similarly, patients with autoimmune thyroiditis have experienced reduced thyroid peroxidase antibody levels with a 12-month intake of 200 μg selenium through selenium-rich yeast.[63] Moderate selenium intake supports overall health, but excessive supplementation may cause toxicity. Studies in animals and certain human trials have demonstrated that daily intake of selenium exceeding 300 μg can increase oxidative stress and impair glucose tolerance.[64] Symptoms of selenium toxicity, such as nausea, vomiting, hair loss, and nail deformities, may appear with prolonged excessive intake of more than 400 μg/day.[65] Research has indicated a potential association between selenium supplementation and a heightened risk of certain cancers, such as prostate cancer, as well as diabetes.[66] Specific populations, including pregnant and lactating women, should be cautious to ensure that they do not exceed the recommended safe dosage of selenium. Differences in individual tolerance to selenium, influenced by genetic factors, highlight the importance of assessing serum selenium levels before initiating supplementation to minimize potential health risks.[67] Further investigation is required to comprehend how selenium interacts with other nutrients and medications in managing PCOS, aiming to prevent adverse reactions and drug interactions.[51]

The ideal dosage and duration for selenium supplementation have yet to be established. The wide range of selenium dosages and supplementation durations used in different studies has led to inconsistent results, making it challenging to determine an optimal supplementation regimen for patients with PCOS. Targeted research is crucial for informing clinical practice. At present, there is a lack of extensive, long-term research clarifying the safe selenium dosage for pregnant and lactating women, as well as its long-term impact on maternal and infant metabolism. Future research should concentrate on establishing dosage thresholds for different physiological stages within this population and examining the effects on both maternal and infant generations. Furthermore,

individual differences in selenium metabolism and requirements exist. A standardized protocol for detecting serum selenium levels and individualized criteria for determining appropriate levels have yet to be developed. In addition, research on the influence of gene polymorphisms associated with selenium metabolism on tolerance is limited. Therefore, developing personalized selenium supplementation plans tailored to individual genetics, nutritional status, and other factors is a crucial challenge to address. Future advancements necessitate the development of precise supplementation tools, which can be achieved by integrating serum selenium measurement with genetic analysis. There is a significant lack of in-depth research on the interactions between selenium and other nutrients, such as Vitamin D and zinc, as well as pharmaceuticals like metformin, in the management of PCOS. It is imperative to elucidate the synergistic or antagonistic effects of these interactions and determine the necessary dosage adjustments.

7. Conclusion

Despite the progress made in understanding the relationship between selenium and PCOS, there are still many unanswered questions surrounding this topic. Specifically, the exact role that selenium plays in the development of PCOS remains unclear. Although selenium is associated with oxidative stress, inflammation, hormone regulation, and other processes, further investigation is required to elucidate its specific effects on these mechanisms and the interactions among various signaling pathways. For example, it is unclear whether selenium directly affects the insulin signaling pathway or indirectly reduces oxidative stress and inflammation, thereby influencing insulin resistance.[29] Personalized medicine, a rapidly advancing field, holds significant potential for future healthcare improvements, including the application of selenium in the treatment of PCOS. Future research should aim to develop personalized selenium supplementation strategies based on individual genetic profiles to improve therapeutic outcomes for patients with PCOS.

In the clinical practice of personalized treatment, the application of selenium, despite its critical importance, encounters several practical challenges. These include inadequate correlation of indicators, lack of standardized methodologies, and technical deficiencies in detecting selenium levels in special populations. The precision in dose individualization for supplementary treatment remains insufficient, safety control is challenging, and the interactions among combination drugs are not well understood. Furthermore, systemic obstacles, such as non-standardized diagnostic and treatment pathways, insufficient support from primary healthcare, and limited evidence-based data, hinder the effective implementation of selenium detection and supplementation. Therefore, targeted solutions are urgently required to overcome these bottlenecks. Genome-wide association studies can identify genetic variations in selenium metabolism, enabling the development of personalized selenium supplementation plans to improve treatment efficacy and safety. This individualized method could transform PCOS treatment and enhance the quality of life for affected patients.[68]

Selenium has emerged as a promising focus for further research and potential clinical applications in the treatment of PCOS within medical studies. Exploring the intricate role of selenium in PCOS could lead to the development of more precise and effective treatment strategies. Modern technologies such as gene editing and cellular models offer the opportunity to delve deeper into selenium-related signaling pathways and identify key molecular targets, paving the way for innovative selenium-based therapies. Large-scale randomized controlled trials are crucial to establishing the optimal dosage, treatment duration, and target population for selenium supplementation in managing PCOS. Comprehensive studies can facilitate the formulation of personalized treatment plans, thereby enhancing the quality of life and reproductive outcomes for individuals with PCOS. Further exploration of selenium's potential in PCOS management holds great promise for the future of medical advancements.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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Ethics approval and consent to participate

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