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Interplay of Serum Zinc, Insulin Resistance and PCOS: A Mini Review

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Abstract

Polycystic Ovary Syndrome (PCOS) is a multifactorial endocrine disorder affecting women of reproductive age, characterized by hyperandrogenism, oligo/anovulation, and insulin resistance. It is closely associated with obesity, chronic inflammation, and metabolic disturbances. Among various contributing factors, recent research underscores the pivotal role of trace elements, particularly zinc, in both the development and management of PCOS. Zinc plays a crucial role in numerous biological processes, including insulin synthesis, secretion, and stabilization, as well as modulating its receptor activity. It also functions as a cofactor for antioxidant enzymes, mitigating oxidative stress and reducing inflammation-key contributors to the progression of PCOS. Studies consistently show that women with PCOS tend to have lower serum zinc levels compared to healthy controls, with a strong negative correlation between zinc levels and Body Mass Index (BMI). Zinc supplementation has demonstrated potential benefits in improving insulin sensitivity, fasting glucose, lipid profiles, and hormonal imbalances while reducing markers of oxidative stress and inflammation. However, discrepancies in findings regarding serum zinc levels may result from variations in study methodologies, population demographics, dietary zinc intake, and comorbidities. Future research should prioritize large-scale, longitudinal studies to establish optimal zinc dosages and investigate its synergistic effects with other therapeutic interventions, such as lifestyle modifications, dietary adjustments, and pharmacological treatments. A better understanding of zinc's biochemical mechanisms may lead to innovative strategies for managing PCOS, alleviating its metabolic and reproductive complications, and improving overall quality of life for affected women.

Keywords: Polycystic Ovary Syndrome (PCOS); Insulin Resistance; Zinc Deficiency; Oxidative Stress; Glucose Homeostasis

Abbreviations

PCOS: Polycystic Ovary Syndrome; BMI: Body Mass Index; ZnT-8: Zinc Transporter 8; ROS: Reactive Oxygen Species; NF-κB: Nuclear Factor Kappa B; CAT: Catalase; GPx: Glutathione Peroxidase; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; PRL: Prolactin.

Introduction

Polycystic Ovary Syndrome (PCOS)

PCOS is a prevalent endocrine disorder affecting 5-10% of women of reproductive age [1]. It is characterized by chronic abnormal ovarian function and hyperandrogenism. The diagnosis is established when two of the following three criteria are met: (1) oligo- or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism, or (3) polycystic ovaries identified through imaging, provided no other etiology explains the symptoms [1].

Women with PCOS often experience menstrual irregularities such as oligo- or amenorrhea and anovulatory infertility. Hyperandrogenism manifests as hirsutism, persistent acne, and androgenetic alopecia. Obesity, a common comorbidity, exacerbates the clinical and metabolic manifestations of the syndrome. Without timely diagnosis and management, PCOS can lead to significant long-term health risks, including metabolic disturbances like diabetes mellitus, dyslipidemia, and hypertension [2]. Cardiovascular disease and endometrial carcinoma are also potential complications [2].

A hallmark feature of PCOS is insulin resistance, which may be present in both obese and non-obese individuals with the condition. Elevated fasting insulin levels and impaired glucose tolerance (IGT) are common findings, underlining the central role of insulin dysregulation in PCOS pathophysiology [3]. South Asian women are particularly susceptible to insulin resistance at lower body mass index (BMI) thresholds compared to Caucasian women, and a BMI >25 kg/m^2 warrants glucose tolerance assessment in this population [4].

Insulin secretion by pancreatic β-cells relies on zinc, which forms insulin hexamers around Zn^{2+} ions, facilitated by the ZnT-8 transporter as shown in Figure 1. Zinc plays a crucial role in insulin stabilization, receptor binding, and delayed absorption.

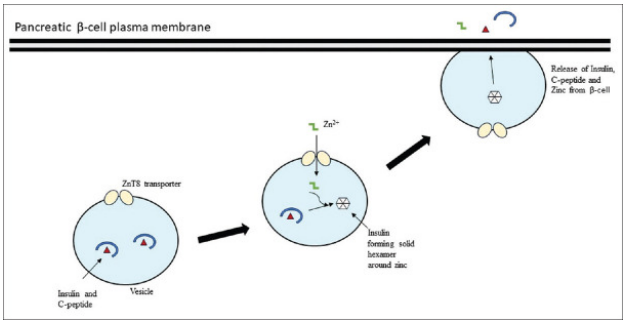

Figure 1: Figure showing Insulin secretion and role of ZnT-8 and zinc ions (Zn2+) in the pancreatic beta cell.

Zinc and its Effect on Insulin Resistance and Inflammation Affecting PCOS

Zinc is vital for immune function, modulating inflammation, oxidative stress, and immune response. It supports neutrophil extracellular traps (NET) formation and promotes cell-mediated over humoral immunity such dysfunctions lead to a worse outcome in the response towards bacterial infection and sepsis. For instance, zinc is an essential component of the pathogen-eliminating signal transduction pathways leading to neutrophil extracellular traps (NET[5]. Zinc reduces proinflammatory responses by targeting NF-κB and enhances antioxidant defense through metallothioneins, glutathione, and catalase activation. It stabilizes protein sulfhydryls and inhibits metal-catalyzed oxidative reactions. Zinc deficiency heightens inflammation and oxidative damage, while supplementation reduces NF-κB activation [6] and proinflammatory cytokines like TNF-α [7]. This highlights Zinc's dual antioxidant and anti-inflammatory roles in maintaining immune and cellular homeostasis.

Moti, et al. suggest that elevated oxidative stress and reduced antioxidant capacity may contribute to the higher risk of cardiovascular disease in women with PCOS, alongside well-established risk factors like insulin resistance, hypertension, central obesity, and dyslipidemia [8]. Since ROS generation is closely linked to androgen levels, these findings imply that oxidative stress driven by ROS might play a role in the development of both insulin resistance and hyperandrogenism in PCOS [9]. Additionally, the increased percentage of truncal fat indicates that higher abdominal adiposity could be a significant factor contributing to ROS-induced oxidative stress in obese women with PCOS, as well as a potential modulator of insulin function in these individuals [9]. The enhanced production of ROS is thought to be one of the contributing factors in the development of PCOS, as it leads to lipid peroxidation and damage to cell membranes [9]. The redox imbalance in PCOS is reflected in the reduced activity of antioxidants like catalase (CAT) and glutathione peroxidase (GPx), as well as elevated biomarkers of oxidative stress such as malondialdehyde (MDA) concentrations [10].

Emerging research has highlighted a potential link between PCOS and disturbances in trace elements, particularly zinc [11]. Zinc, an essential trace element, serves critical functions in enzymatic activity, protein stabilization, and antioxidant defense. It supports insulin synthesis, crystallization, and storage in pancreatic β-cells through the Zinc Transporter ZnT8 [12]. Zinc also inhibits glycogen synthase kinase 3 (GSK3), a key enzyme regulating glycogen metabolism, exhibiting insulin-like effects [13]. The literature describing the correlation between Zinc and PCOS levels will be reviewed in this article.

Discussion

Several studies suggest lower serum zinc levels in women with PCOS compared to controls [10,14], though some findings report no significant differences [15]. Zinc supplementation has demonstrated improvements in glucose homeostasis, insulin sensitivity, and lipid profiles, with reductions in triglycerides and VLDL cholesterol [16]. The link between insulin resistance in PCOS and zinc deficiency underscores the potential role of zinc in managing the metabolic aspects of this syndrome [11]. PCOS has a multifactorial etiology, with insulin resistance playing a pivotal role in its pathogenesis. The interplay between trace elements like zinc and metabolic dysfunction in PCOS warrants further exploration. Understanding these mechanisms could open avenues for novel therapeutic strategies, including trace element supplementation, to improve outcomes for women with PCOS. A meta-analysis by Abedini, et al. [11], which reviewed studies on zinc levels in PCOS published between 2012 and 2017, analyzed data from 1016 participants, including 552 women with PCOS and 464 healthy controls. The findings revealed significant differences in serum zinc levels between PCOS patients and healthy individuals. However, considerable variability was observed across the studies. To address this, the authors performed a subgroup analysis, which indicated that the heterogeneity was reduced when categorized by BMI. Notably, only one study, by Kurdoglu, et al. [17], did not show an association between zinc levels and PCOS. In that study, the mean serum zinc level was higher in PCOS patients than in controls ($p < 0.05$), though the levels were within the normal range (0.60–1.10 mg/mL). Since this was the only study reporting higher zinc levels in PCOS patients, the authors considered other studies. Upon review, it was found that the Kurdoglu, et al. [17] study included participants with a relatively low average BMI of 21 kg/m^2, which was lower than in other studies, making it less reliable as an indicator. Additionally, the study had a small sample size of only 35 cases and 30 controls.

In contrast, one study found no significant difference in zinc levels between women with PCOS and healthy controls [18]. Kanfichian et al. reported lower zinc and selenium levels in the PCOS group compared to the control group [14]. Similarly, Guler, et al. [19] and Zheng, et al. [20] observed significantly lower serum zinc levels in PCOS patients than in controls. These studies also found a negative correlation between serum zinc levels and HOMA-IR, as well as a positive correlation between insulin levels and the glucose/insulin ratio (GIR) [14]. Kanfichian, et al. [14] further emphasized that accurate measurement of zinc levels and understanding their effects on women with PCOS could help improve their nutritional patterns and lifestyles. However, the study's findings may be questioned due to its small sample size (60 cases and 90 controls), which could limit the reliability of the results. Additionally, considering insulin levels and using more robust methodologies would have improved the evaluation.

Chakraborty, et al. [21] conducted a study involving 132 women with PCOS and 46 controls, finding significantly lower zinc levels in the PCOS group ($p<0.04$). Similarly, Ozer, et al. [10] found that zinc levels were notably lower in 71 women with PCOS compared to 53 controls ($p=0.016$), with the lowest levels observed in those with insulin resistance. Farhood, et al. [15] demonstrated a significant negative correlation between serum zinc levels and BMI in women with PCOS. Additionally, they observed an inverse relationship between BMI, prolactin (PRL), and elements such as arsenic, cadmium, copper, lead, manganese, molybdenum, and zinc. Mantzoros, et al. [22] also showed that serum zinc concentration is positively correlated with leptin levels, a finding supported by Farhood, et al. [15]. Zinc deficiency may contribute to leptin resistance in obesity by either directly affecting leptin gene expression or indirectly enhancing leptin production through increased glucose usage in adipose tissue. In this study, a significant negative correlation was also found between serum zinc and PRL levels in non-obese PCOS patients, which is consistent with several in vitro studies showing an inverse relationship between zinc and PRL. Zinc is believed to influence PRL synthesis, storage, release, and peripheral action by interacting with calcium channels, adenylate cyclase, and secretory granules [23]. However, the lack of BMI matching in the study groups may have impacted the significance of the zinc values. Foroozanfard, et al. [16] found that zinc supplementation improved glucose homeostasis and reduced serum triglycerides and VLDL cholesterol levels in women with PCOS.

These studies have shown that serum zinc levels are significantly lower in women with PCOS compared to healthy controls. One potential mechanism linking zinc to PCOS may be its impact on the insulin signaling system. Research indicates that insulin resistance in PCOS is primarily due to defects in insulin action after receptor activation [14]. Clinical and epidemiological studies have suggested that lower zinc status is associated with insulin resistance [24]. Additionally, zinc supplementation has been shown to improve insulin resistance in women with PCOS [16]. It is important to note that between 40-80% of women with PCOS are obese, and the majority are either overweight or obese [2]. Some studies have also reported a negative correlation between serum zinc levels and BMI, both in healthy individuals and in women with PCOS [15,25]. Therefore, one possible explanation for the higher zinc levels found in Kordouglu's study could be the lower BMI range in both the PCOS and control groups compared to participants in other studies.

Previously, studies by Torkanlou, et al. [26] and Di martino, et al. [27] have already shown that obesity is associated

with lower serum zinc levels. A major strength of the study Torkanlou, et al. [26] was that it was carried out in a large number of samples, suggesting that prevention and treatment of people with obesity should lead to the reduction in the prevalence of obesity-related diseases. Additionally, it is possible that other lifestyle characteristics such as diet including taking supplements for zinc and other micronutrients have a positive influence on the outcome. In a previous study by Rios-lugo, et al. [28] showed a negative correlation between BMI and serum Zinc levels ($r = -0.663$ and $p < 0.001$) in both male and female. Another Korean study on metabolic syndrome patients has shown decreased zinc levels with increasing BMI of the population [29]. Another study documented a positive correlation between BMI and fasting insulin levels in both the cases (r = 0.227, p-value = 0.112) and controls (r = 0.612, p-value < 0.0001) [30]. However, significant correlation was only found in the control group. In a previous meta-analysis done by Pearsey, et al. [31] has shown that zinc as an important element in a glycoprotein responsible for dysglycemia and insulin resistance.

Zinc plays a crucial role in metabolism and thermoregulation in obese individuals. Di Martino et al. conducted a study to assess serum zinc levels in obese patients before and after following a severe hypocaloric diet, while also examining its correlation with body mass index (BMI) [27]. Participants adhered to a strict hypocaloric diet (737 Kcal) for 60 days. The study found that serum zinc levels in obese patients were significantly lower ($p < 0.01$) compared to controls, and their BMI was significantly higher. After completing the diet, both serum zinc and BMI levels normalized. These findings suggest a potential relationship between serum zinc levels and the anabolic and catabolic processes associated with obesity [27]. A table displaying serum zinc values in both PCOS patients and controls can be found in Table 1.

Study	Serum Zinc levels (PCOS)	Serum Zinc levels Normal Population	p-value
Farhood, et al. [15]	(n=40) 75.31±33.91	(n=40) 83.8±10.11	0.133
Kanafchian, et al. [14]	(n=60) 81.33 ± 24.28	(n=90) 108.31 ± 63.29	0.022*
Kurduglo, et al. [17]	(n=35) 0.92 + 0.20	(n=30) 0.77 + 0.19	0.006*
Dhar, et al.[30]	(n=50) 122.00 + 26.72	(n=50) 134.89 + 23.06	0.012*
Zheng, et al. [20]	(n=96) 843.46	(n=105) 891.15	0.009*
Guler, et al. [19]	(n=53) 66.3 ± 13.2	(n=33) 78.1 ± 14.7	<0.001*

Table 1: Comparison of Mean Serum Zinc Levels in PCOS and Normal Group in Different Studies.

Conclusion

This review highlights that zinc levels are significantly lower in individuals with polycystic ovary syndrome (PCOS). Zinc deficiency may contribute to the inflammatory processes that are commonly observed in PCOS patients, further exacerbating the condition. As zinc plays a crucial role in regulating insulin sensitivity, its deficiency may also be a contributing factor to the endocrinological abnormalities, such as insulin resistance, frequently seen in PCOS. The relationship between zinc and metabolic disturbances in PCOS underscores the need for a better understanding of its role in this condition. Furthermore, while zinc levels are negatively correlated with obesity and insulin resistance in the general population, the same does not seem to apply to individuals with PCOS. In PCOS patients, zinc levels are already lower, suggesting that factors like obesity and insulin resistance do not appear to influence zinc status in these individuals to the same extent as in the general population. Therefore, the observed lower zinc levels in PCOS patients might be an intrinsic feature of the disorder, rather than a consequence of obesity or insulin resistance alone. This further emphasizes the need to explore zinc supplementation as a potential therapeutic approach in managing PCOS.

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None

Conflict of interest

Authors declare no conflict of interests

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