

ORIGINAL RESEARCH

PERIOPERATIVE MEDICINE

Evaluation of some trace elements and their correlation with sex hormones in women with polycystic ovary syndrome

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ABSTRACT

Background & objective: Polycystic ovary syndrome (PCOS) is one of the most common hormonal conditions affecting women of reproductive age. Its main features include anovulation, polycystic ovaries, and androgen excess. This study aims to investigate the levels of some trace elements in women with PCOS and their correlation with female sex hormones.

Methodology: The present study examined some trace elements, such as magnesium (Mg), zinc (Zn), and copper (Cu) levels, and sex hormones (luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, and prolactin) levels of 60 women patients diagnosed with PCOS and of 30 healthy women.

Results: The results showed that Cu levels had significantly increased, while the Mg and Zn concentrations had decreased in women patients diagnosed with PCOS. Additionally, a notable increase in LH, total testosterone, and prolactin was observed, along with a decrease in FSH for the patient with PCOS compared to the control group.

Conclusion: This study suggests potential associations between Mg, Zn, Cu, the ratio of Cu to Zn, and PCOS in women. Notably, most of these trace elements were significantly correlated with sex hormones (LH, FSH, total testosterone, and prolactin), which affected fertility.

Abbreviations: FSH: follicle-stimulating hormone, LH: luteinizing hormone, PCOS: Polycystic ovary syndrome,

Keywords: Polycystic ovary syndrome, Zinc, Copper, sex hormone.

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1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a hormonal disorder resulting from an endocrine dysfunction that is common in about 5-10% of women of reproductive age.¹

If two of the three criteria listed below are met, it can be diagnosed: (a) biochemical and/or clinical hyperandrogenism; (b) persistent anovulation and/or oligomenorrhea; and/or (c) polycystic ovaries on transvaginal ultrasound.² Metabolic issues such as obesity,

dyslipidemia, and insulin resistance (IR) are linked to PCOS.³ The disorder's significant variety is a reflection of its yet unclear etiology and pathophysiology. Thus, genetic, environmental, and behavioral factors combine to cause PCOS, which is considered a complicated multifactorial condition.⁴ Oxidative stress may potentially contribute to the pathophysiology of PCOS by causing IR and hyperandrogenism, according to mounting evidence.⁵ The importance of minerals for female reproductive function has been well-documented. Minerals are specifically linked to hormone regulation, metabolism, and ovulation. Human cells contain different concentrations of more than 60 minerals. Each of them contributes significantly to a number of bodily functions.⁶

Minerals operate as molecules or coordinators of certain cellular processes in key bodily tissues and are constituents of enzymes or cofactor that regulate a broad variety of energy and metabolic events.⁷ Their relationship is the most crucial aspect.⁸ Serum concentrations of mineral in human,⁹ or in animal models,¹⁰ have formed the basis for the majority of research to date on minerals and reproductive function, particularly reproductive hormones. Normal biological processes depend on trace minerals including zinc (Zn), copper (Cu), and magnesium (Mg), which are also important in metabolic pathways involving enzymes, hormones, and vitamins.¹¹ Metabolic dysfunction is a hallmark of PCOS, and there is substantial evidence linking aberrant levels of trace elements to metabolic syndrome.¹² The fundamental micronutrients include Cu, Zn, and Mg in addition to a several proteins and metalloenzymes that are necessary for cellular metabolism and oxidative stress pathways.

The primary antioxidants in the first enzymatic step are glutathione-dependent enzymes and superoxide dismutase (SOD); manganese SOD (Mn-SOD or SOD2) is located in the mitochondria, whereas copper-zinc SOD (Cu, Zn-SOD or SOD1) is situated in the cytosol.¹³ One of the cations involved in energy conversions in the human body and controls the appropriate direction of hormone responses and insulin production is magnesium. Extracellular Mg^{2+} competitively inhibits the inflow of Ca^{2+} , which starts the production of insulin. The inverse relationship between serum Mg^{2+} and serum-insulin concentrations might be explained by this. Type-2 diabetes and other metabolic disorders that follow women with PCOS are closely associated with magnesium.¹⁴

One of the vital trace elements for the human body, copper (Cu) acts as a cofactor in enzymes and as a stabilizer and structural component for hormonal activity.¹⁵ Cu content in serum has been discovered to be associated with certain artery wall structural

abnormalities, stress, infection, and type 2 diabetes mellitus.¹⁶ Cu has estrogen-like action, according to studies.¹⁷ Cu has been shown to significantly affect reproductive function by disrupting the development of embryos and interfering with the reproductive systems of both sexes.¹⁸ The structure, regulation, and catalytic activity of more than 300 proteins, transcription factors, and enzymes depend on zinc, a crucial trace element. Complications from zinc deficiency in females include aberrant ovarian development and decreased production and release of LH and FSH.¹⁹ Thus, this study aims to assess serum some trace elements (Mg, Cu, and Zn) levels and correlation with the levels of female sex hormones in PCOS patients and may also explain the association between trace elements and PCOS status in these individuals.

2. METHODOLOGY

This research is a case-control design. The samples were obtained between November 2024 to March 2025 from the "infertility center" at Al-Sader Medical City, Al-Najef Governorate, Iraq. Ethical approval was obtained from the University of Kufa and Al-Najef Health Directorate (No.4565, November 13th, 2024). Patient samples were also collected from a private clinic. A study consists of 90 females of reproductive age (20–40 year); 60 diagnosed with PCOS (married and had not been pregnant for at least one year after marriage) and 30 healthy females with matching ages, weight, height, and body mass index. According to the Rotterdam (ESHRE/ASRM), all patients diagnosed by a gynecologist on day 12 of their menstrual cycle underwent an ultrasound examination. The physician looked for at least two of these three symptoms to diagnose PCOS in women:

1. Menstrual irregularities or absence due to ovulation (amenorrhea or oligomenorrhea).
2. Clinical androgen excess (hirsutism, acne).
3. Ultrasound revealed multiple small ovarian cysts.

The subjects were excluded if they had experienced any infections or chronic illnesses like dyslipidemia, diabetes, hypertension, cardiovascular disease, renal or thyroid dysfunction, Cushing's syndrome, androgen-secreting tumors, or smoking.

Fasting blood samples (5 mL) were obtained from the vein during the follicular phase of the menstrual cycle (2nd–3rd day). After 15 minutes, the blood sample was centrifuged at 3000 xg for 10 minutes. Serum was stored at $-20^{\circ}C$ until analysis. Fluorescence immunoassay was employed to assess the levels of serum LH, FSH, total

Table 1: Demographic characteristics of the participating PCOS patients and healthy controls

Variables	PCOS patients (n = 60)	Healthy controls (n = 30)	P-value
Age (Years)	28.812 ± 6.578	29.166 ± 4.678	< 0.761
Weight (kg)	63.516 ± 14.531	63.125 ± 13.799	< 0.647
Height (m)	1.639 ± 0.039	1.632 ± 0.0428	< 0.099
BMI (kg/m ²)	23.612 ± 5.964	23.904 ± 6.615	< 0.104
Duration of disease (Years)	3.663 ± 0.843	-----	-----

Results expressed as mean ± standard deviation; P < 0.05 was considered significant; BMI: Body Mass Index.

Table 2: Comparison of female sex hormone levels between PCOS patients and healthy controls.

Variables	PCOS patients (n = 60)	Healthy controls (n = 30)	P-value
LH (mIU/mL)	7.197 ± 2.779	5.886 ± 1.385	< 0.0036
FSH (mIU/mL)	5.151 ± 1.402	6.978 ± 2.308	< 0.0001
LH/FSH ratio	1.596 ± 0.699	0.881 ± 0.138	< 0.0001
Total testosterone (g/mL)	3.639 ± 1.164	2.556 ± 0.896	< 0.0001
Prolactin (ng/mL)	4.405 ± 0.589	2.921 ± 0.362	< 0.0001

Results expressed as mean ± standard deviation; ; P < 0.05 was considered significant; FSH: Follicular-Stimulating Hormone, LH; Luteinizing Hormone.

Table 3: Comparison of some trace element levels between PCOS patients and healthy controls.

Variables	PCOS patients (n = 60)	Healthy controls (n = 30)	P-value
Mg (mg/dL)	1.521 ± 0.131	1.745 ± 0.196	< 0.0001
Cu (µg/dL)	121.421 ± 36.659	109.111 ± 28.823	< 0.0001
Zn (µg/dL)	55.953 ± 13.456	85.395 ± 21.361	< 0.0001
Cu/Zn ratio	2.331 ± 0.773	1.304 ± 0.311	< 0.0001

Results were expressed as mean ± standard deviation; P < 0.05 was considered significant; Mg: Magnesium, Cu: Copper, Zn: Zinc.

testosterone, and prolactin using ichroma™. Body mass index (BMI) was calculated by using the formula: BMI = weight (kg)/ height² (meters²).¹⁹ Serum levels of magnesium, zinc and copper were measured using the zinc assay kit and the copper assay kit by Biolabo, Maizy, France.

2.1. Statistical Analysis

To determine the distribution types of the results, the Kolmogorov-Smirnov test was used. The student t-test

was employed to assess differences in scale variables between diagnostic categories. The results were expressed as (mean ± standard deviation) for normally distributed values. For the correlation study, Pearson's correlation coefficients (r) examine the association between the scale variable to find out the correlation between the parametric parameter and the other variable. Statistical significance was determined for all hypothesis tests with P-values less than 0.05 (two-tailed). IBM's Statistical Package for Social Sciences, version 26 (SPSS, Chicago, Illinois, USA), was used to compile and analyze the data.

3. RESULTS

Table 1 provides a summary of the general demographics of the females who participated in this study. As shown in Table 2, the results indicated that patients with PCOS had significantly (P < 0.0001) higher levels of LH, FSH, LH/FSH ratio, total testosterone, and prolactin, except that FSH was reduced compared to the healthy control group. Furthermore, patients with PCOS had especially (P < 0.01) reduced Mg and Zn levels. In contrast, Cu and Cu/Zn levels were statistically increased (P < 0.01), as illustrated in Table 3. The correlations of Mg, Cu, Zn, and the Cu/Zn ratio with other parameters are presented in Table 4. Mg, Cu, Zn, and the Cu/Zn ratio were significantly positively correlated with all studied parameters and between them, except for Cu, and the Cu/Zn ratio with total testosterone and Zn, but non-significant negative correlation between Cu/Zn ratio with Zn and total testosterone.

Table 4: Correlation analysis of trace element levels with studied parameters in patients with polycystic ovary syndrome.

Parameters		Mg	Cu	Zn	Cu/Zn ratio
Age (Years)	r	0.633**	0.634**	0.548**	0.406**
	P-value	0.0001	0.0001	0.0001	0.001
Weight (kg)	r	0.464**	0.490**	0.538**	0.518**
	P-value	0.0001	0.0001	0.0001	0.0001
Height (m)	r	0.477**	0.542**	0.539**	0.493**
	P-value	0.0001	0.0001	0.0001	0.0001
BMI (kg/m ²)	r	0.379**	0.364**	0.440**	0.456**
	P-value	0.003	0.004	0.0001	0.0001
Duration of disease (Years)	r	0.545**	0.413**	0.476**	0.453**
	P-value	0.0001	0.001	0.0001	0.0001
LH (mIU/mL)	r	0.486**	0.266*	0.488*	0.308*
	P-value	0.0001	0.040	0.0001	0.017
FSH (mIU/mL)	r	0.334**	0.478**	0.521**	0.388**
	P-value	0.009	0.0001	0.0001	0.002
LH/FSH ratio	r	0.565**	0.325*	0.423**	0.437**
	P-value	0.000	0.011	0.001	0.0001
Total testosterone (ng/mL)	r	0.484**	0.043	0.701**	-0.240
	P-value	0.0001	0.746	0.0001	0.065
Prolactin (ng/mL)	r	0.410**	0.505**	0.560**	0.383**
	P-value	0.0001	0.0001	0.0001	0.003
Mg (mg/dL)	r	1	0.452**	0.610**	0.284*
	P-value		0.0001	0.0001	0.028
Cu (µg/dL)	r	0.452**	1	0.218	0.790**
	P-value	0.0001		0.095	0.0001
Zn (µg/dL)	r	0.610	0.218	1	-0.072
	P-value	0.0001	0.095		0.583
Cu/Zn ratio	r	0.284*	0.790**	-0.072	1
	P-value	0.028	0.0001	0.583	

*. Correlation is significant at the 0.05 level (2-tailed); **. Correlation is significant at the 0.01 level (2-tailed); r: Pearson correlation coefficient.

4. DISCUSSION

One of the major endocrine disorders producing difficulties in women's reproduction is polycystic ovarian syndrome, which has a complex origin and a variety of clinical characteristics.²⁰ The creature must have trace essential elements in order to survive. They either serve as cofactors to support certain an organism's essential functions or directly start or affect specific physiological processes. The impact of trace elements in PCOS, however, is not well supported by data. This study looked at the essential elements and PCOS.

Interestingly, the majority of trace elements showed a linear increase in the incidence of PCOS, perhaps as a result of their deficiency being more strongly linked to delayed follicular maturation in PCOS patients.²¹

Subsequent research verified that deficits in trace elements like zinc and selenium were often seen and raised the complication of PCOS in women. By influencing hormone production and folliculogenesis through compromised mitochondrial activity and autophagocytosis, zinc deficiency contributes to PCOS.²²

Hormonal conditions like hyperandrogenism are very frequently seen in women with PCOS. In comparison to women without PCOS, the authors of several investigations observed such anomalies as substantial elevations in total testosterone, free testosterone, and dehydroepiandrosterone concentrations.^{23,24} However, it is still unknown how zinc supplements affect the hormonal balance of PCOS-afflicted women, particularly about testosterone levels. It is considered that hyperandrogenism in PCOS is mostly created by increased androgen production in the ovaries, adrenal glands, and peripheral tissues. Additionally, PCOS is linked to a noticeable rise in 5 α -reductase global activity, which enhances the androgenic effects caused by peripheral target cells converting testosterone to dihydrotestosterone.²⁵ Zinc is regarded as an anti-androgen because it inhibits 5 α -reductase, which lowers the amount of dihydrotestosterone produced.²³ Inhibiting aromatase (which reduces the conversion of testosterone to estradiol) and enhancing the conversion of androstenedione to testosterone are two of its other roles in androgen metabolism.^{23,26}

Furthermore, it was demonstrated that zinc shortage disrupted the angiotensin converting enzyme's function, which appears to be connected to the production of adrenal androgens. Zinc can also influence the function of androgens since the DNA-binding region of the androgen receptor is a zinc finger protein, and it has been demonstrated that zinc shortage inhibits the activity of this receptor.²⁷ Hirsutism is a consequence of hyperandrogenism and has also been noted in PCOS-afflicted women. Nevertheless, there is no correlation between plasma zinc levels and hirsutism. Hormonal imbalances in women with PCOS were also linked to changes in LH, FSH, and prolactin concentrations; however, the direction of these changes was unclear and in some studies, they were statistically insignificant.^{28,29} These changes also occurred after taking zinc sulfate supplements.

The element magnesium is vital to human health. The mean serum magnesium concentration in PCOS patients was increased than that in healthy controls ($p < 0.0001$), and there was a link between the levels and the other trace elements we tested in our study, including age, BMI, testosterone, LH, and FSH. even though Muneyyirci-Delale *et al.* found lower levels in PCOS woman,³⁰ which is consistent with our study's findings, Kauffman *et al.*²⁰

Cu plays a complicated function in PCOS and can change depending on the phenotype. While some studies have observed no differences from the control group, others have found higher Cu levels in PCOS patients. When metabolic parameters were taken into account, both obese and non-obese PCOS patients had

significantly higher blood Cu levels than healthy participants,³² and this increase was associated with IR. As a result, Cu restriction in these individuals has been suggested as a possible tactic to reduce oxidative stress and IR that this metal may induce, as well as to reduce long-term metabolic issues.³³ Cu levels were lower in PCOS patients than in the control group, which is consistent with a previous study,⁴ although another investigation found that women with PCOS and IR had greater Cu concentrations than in those without IR. Cu concentrations in the fluid of the follicles were greater in PCOS females than in healthy individuals,³⁴ which may have an adverse effect on follicle growth and be linked to abnormalities in steroidogenesis.

Other researchers consistently discovered that consumption of copper was positively associated with the incidence of PCOS and that the metal changed ovarian steroid production, influencing the creation of ovarian follicles, causing premature follicular atresia, and preventing follicular ripeness and multiple follicle consistency. The structure, regulation, and catalytic activity of more than 300 proteins, transcription factors, and enzymes depend on zinc, a crucial trace element. Complications from zinc deficiency in females include aberrant ovarian development and decreased FSH and LH production and secretion.¹⁹ It was known that supplementing insulin with zinc would increase the efficiency of a certain insulin dosage before proof of a connection between zinc and insulin in the β cell surfaced. Zinc was added *in vitro* to insulin when it was first given to treat type 1 diabetes in order to prolong its effects by postponing its absorption from the injection site. Because zinc is a strong antioxidant, its shortage increases oxidative damage to the heart and several organs; its impact on oxidative stress may be one of the potential reasons of zinc's association with PCOS, other than problems in the insulin signaling pathway.

5. CONCLUSION

The current study exhibited a notable decline in magnesium and zinc levels in patients with PCOS, while copper and Cu/Zn ratio levels increased. According to this study, it was impacted by both high and low fertility hormones.

6. Acknowledgement

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7. Data availability

The numerical data generated during this research are available from the authors.

8. Conflict of interest

All authors declare that there was no conflict of interest.

9. Funding

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Ethical considerations

Ethical approval was obtained from the University of Kufa and Al-Najef Health Directorate (No.4565, November 13th, 2024).

11. Authors' contribution

HAT: writing the manuscript

MAK, MMM: conduction of the study work and manuscript editing

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