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ZINC AND COPPER LEVELS AND THEIR CORRELATION WITH POLYCYSTIC OVARIAN SYNDROME BIOCHEMICAL CHANGES

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder characterized by oligo-anovulation, clinical or biochemical hyperandrogenism, and/or polycystic ovarian morphology. It affects approximately 4–8% of women of reproductive age and is frequently associated with obesity, insulin resistance, and infertility. Trace elements such as zinc and copper are involved in metabolic regulation, insulin function, oxidative stress, and inflammatory pathways, which may contribute to the pathophysiology of PCOS. **Aim:** To evaluate the association between serum zinc and copper levels and PCOS. **Methods:** A case–control study was conducted at Al-Zahraa Maternity and Pediatric Teaching Hospital, Najaf, over 11 months (September 1, 2021–August 1, 2022). Fifty women diagnosed with PCOS according to Rotterdam criteria were enrolled as the case group, and 50 healthy women without PCOS served as controls. Serum zinc and copper levels were measured and compared between groups. Clinical characteristics and hormonal profiles were also assessed. **Results:** Women with PCOS had significantly higher body mass index (BMI), increased rates of infertility, irregular menstrual cycles, acne, hirsutism, and depressive symptoms compared with controls. Laboratory findings revealed elevated luteinizing hormone (LH) levels, an increased LH/FSH ratio, and significantly higher serum copper levels in the PCOS group. Serum zinc levels did not differ significantly between groups. A copper cutoff value ≥102.3 mg/dl demonstrated 92% sensitivity and 96% specificity for association with PCOS. **Conclusion:** Serum copper levels are significantly associated with PCOS and may serve as a potential diagnostic biomarker, whereas zinc appears to have limited clinical value in distinguishing PCOS cases from healthy controls.

KEYWORDS: Polycystic ovary syndrome; Zinc; Copper; Insulin resistance; Oxidative stress; Case–control study.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder characterized by oligo-anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology (PCOM).[1] It represents one of the most common endocrinopathies affecting women of reproductive age and has important reproductive, metabolic, and psychological implications.[2] Although originally recognized mainly for its reproductive consequences, increasing attention has been directed toward its long-term metabolic and cardiovascular risks.[3] Infertility is a major concern, with an estimated prevalence of 70–80% among affected women, largely due to chronic anovulation.[4] Diagnostic criteria have evolved over time. The National Institutes of Health/National Institute of Child Health and Human Development (NIH/NICHD) criteria require the presence of hyperandrogenism and menstrual dysfunction after exclusion of related disorders.[5] The Rotterdam consensus broadened the definition by requiring any two of three features: oligo-/anovulation, hyperandrogenism, or polycystic ovaries on ultrasound.[6] The Androgen Excess and PCOS Society emphasized hyperandrogenism as a mandatory component along with ovarian dysfunction.[7] Depending on the criteria used, prevalence estimates range from 4% to 8% with NIH

criteria and may be two to three times higher using Rotterdam criteria.[8] The etiology of PCOS is multifactorial and likely polygenic, with familial aggregation and genome-wide association studies supporting a genetic predisposition.[9] Pathophysiologically, abnormalities in the hypothalamic–pituitary–ovarian axis, insulin resistance, and hyperinsulinemia contribute to increased luteinizing hormone (LH) secretion and enhanced ovarian androgen production.[10] Oxidative stress and low-grade inflammation are also implicated in disease progression.[11] Mineral homeostasis may influence reproductive and metabolic pathways. Zinc is essential for insulin synthesis, secretion, and receptor signaling, and deficiency has been linked to insulin resistance and oxidative imbalance.[12] Copper, a cofactor for antioxidant enzymes such as superoxide dismutase, may contribute to oxidative stress when elevated, potentially promoting inflammation and metabolic disturbances in PCOS.[13] However, evidence regarding trace element alterations in PCOS remains limited and inconsistent. Therefore, evaluating zinc and copper levels may provide further insight into their potential role in the pathogenesis of PCOS.

METHOD

This case–control study was conducted at Al-Zahraa Maternity and Pediatric Teaching Hospital over an 11-month period from 1st September 2021 to 1st August 2022. The study included 100 women of reproductive age, divided into two groups: 50 women diagnosed with polycystic ovary syndrome (PCOS) according to the Rotterdam criteria (case group) and 50 apparently healthy women without clinical, biochemical, or ultrasonographic features of PCOS (control group). Women were eligible if they were within reproductive age and fulfilled the diagnostic criteria for PCOS. Exclusion criteria included active infection, chronic systemic diseases, chronic drug use (including combined oral contraceptive pills), and use of multivitamins or mineral supplements. All participants underwent detailed history taking and clinical examination. Data collection included demographic characteristics, menstrual history, infertility history, past medical and surgical history, and clinical manifestations suggestive of PCOS such as hirsutism, acne, and obesity. Ultrasound examination was performed to assess ovarian morphology. Laboratory investigations included luteinizing hormone (LH), follicle-stimulating hormone (FSH), serum prolactin, total testosterone, lipid profile, random blood sugar (RBS), and serum zinc and copper levels. Diagnosis of PCOS was based on the Rotterdam criteria, requiring at least two of the following after exclusion of other causes: oligo- or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound. Two milliliters of venous blood were collected under aseptic conditions. One milliliter was used for zinc measurement and one milliliter for copper measurement. Samples were collected in heparinized tubes, centrifuged, and plasma was separated. Serum zinc and copper levels were measured using an APEL PD-307 spectrophotometer according to the manufacturer's instructions. Data were analyzed using Microsoft Excel 2016 and IBM SPSS version 26. Descriptive statistics, Chi-square test, Fisher's exact test, Student's t-test, and receiver operating characteristic (ROC) curve analysis were applied. A p-value <0.05 was considered statistically significant.

RESULTS

Table 1 shows the age distribution of participants in both study groups. There was no statistically significant difference between PCOS patients and controls regarding age (P = 0.772). The mean age in the PCOS group (26.3 ± 6.24 years) was comparable to that of the control group (27.36 ± 6.56 years). This indicates that both groups were age-matched, minimizing age as a confounding variable and strengthening the internal validity of the study.

Table 1: Age Distribution.

Age (years)	PCOS n (%)	Control n (%)	Total n (%)
<20	8 (16%)	8 (16%)	16 (16%)
20–25	13 (26%)	13 (26%)	26 (26%)
25–30	12 (24%)	8 (16%)	20 (20%)
30–35	11 (22%)	11 (22%)	22 (22%)
35–40	6 (12%)	10 (20%)	16 (16%)
Mean ± SD	26.3 ± 6.24	27.36 ± 6.56	26.83 ± 6.39

P value = 0.772 (No statistically significant difference between groups).

Table 2 demonstrates a statistically significant difference in BMI between the two groups (P = 0.0001). Women with PCOS had a significantly higher mean BMI (28.57 ± 3.09 kg/m²) compared with controls (25.79 ± 1.74 kg/m²). Notably, 42% of PCOS patients were obese (BMI 30–40 kg/m²), whereas none of the control participants fell within this category. These findings support the strong association between PCOS and increased body weight, suggesting a potential link with insulin resistance and metabolic dysfunction.

Table 2: BMI Distribution.

BMI (kg/m²)	PCOS n (%)	Control n (%)	Total n (%)
18.5–25	11 (22%)	15 (30%)	26 (26%)
25–30	18 (36%)	35 (70%)	53 (53%)
30–40	21 (42%)	0 (0%)	21 (21%)
Mean ± SD	28.57 ± 3.09	25.79 ± 1.74	27.18 ± 2.86

P value = 0.0001 (BMI significantly higher in PCOS group).

Table 3 reveals no significant difference in marital status or family history of PCOS between the groups (P > 0.05). However, infertility was significantly more frequent among women with PCOS (67.4%) compared to controls (26%) (P = 0.0001). Additionally, irregular menstrual cycles were significantly higher in the PCOS group (62%) compared with controls (26%) (P = 0.0001). These findings highlight the classical reproductive disturbances associated with PCOS, particularly anovulation and menstrual dysfunction.

Table 3: Reproductive and Family Characteristics.

Variable	PCOS n (%)	Control n (%)	P value
Infertile	31 (67.4%)	13 (26%)	0.0001
Irregular cycle	31 (62%)	13 (26%)	0.0001
Positive family history	10 (20%)	7 (14%)	0.424

Table 4 demonstrates that clinical manifestations of hyperandrogenism and psychological symptoms were significantly more prevalent among women with PCOS. Hirsutism was present in 90% of PCOS cases compared to only 4% in controls (P = 0.0001), making it the most prominent clinical feature. Acne was also significantly higher in PCOS patients (48% vs. 12%, P = 0.0001). Depression was more common in the PCOS group (60%) compared to controls (30%) (P = 0.003). These results emphasize the multisystem clinical burden of PCOS.

Table 4: Clinical Manifestations.

Symptom	PCOS n (%)	Control n (%)	P value
Hirsutism	45 (90%)	2 (4%)	0.0001
Depression	30 (60%)	15 (30%)	0.003
Acne	24 (48%)	6 (12%)	0.0001

Table 5 shows significant hormonal differences between groups. LH levels were significantly higher in PCOS patients (9.08 ± 1.93 IU/L) compared to controls (6.07 ± 2.11 IU/L) (P = 0.0001). The LH/FSH ratio was also significantly elevated (P = 0.0001), while FSH levels were significantly lower in the PCOS group (P = 0.031). Prolactin levels did not differ significantly (P = 0.074). Regarding trace elements, serum zinc levels were not significantly different between groups (P = 0.373), suggesting limited association with PCOS. In contrast, copper levels were markedly elevated in PCOS patients (131.43 ± 20.72 µg/dl) compared to controls (85.82 ± 10.95 µg/dl) (P = 0.0001), indicating a strong association between elevated copper and PCOS.

Table 5: Hormonal and Trace Element Levels (Mean ± SD).

Parameter	PCOS	Control	P value
LH (IU/L)	9.08 ± 1.93	6.07 ± 2.11	0.0001
FSH (IU/L)	4.06 ± 1.53	4.77 ± 1.68	0.031
LH/FSH ratio	2.78 ± 1.87	1.52 ± 0.95	0.0001
Prolactin	40.73 ± 6.17	38.67 ± 5.22	0.074
Zinc (µg/dl)	91.92 ± 19.39	88.82 ± 14.93	0.373
Copper (µg/dl)	131.43 ± 20.72	85.82 ± 10.95	0.0001

Table 6 presents the diagnostic performance of biochemical markers. Serum copper demonstrated excellent predictive ability with an area under the curve (AUC) of 0.981. At a cutoff value ≥102.3 µg/dl, copper showed 92% sensitivity and 96% specificity, indicating high diagnostic accuracy (94%). LH and LH/FSH ratio showed moderate diagnostic value (AUC 0.847 and 0.787, respectively). FSH, prolactin, and zinc exhibited poor predictive performance (AUC <0.65). These findings suggest that among the evaluated markers, serum copper is the most reliable biochemical indicator associated with PCOS in this study.

Table 6: ROC Analysis and Predictive Ability.

Marker	AUC	Cutoff	Sensitivity	Specificity	Accuracy
LH	0.847	>7.25	74%	68%	71%
FSH	0.624	≤4.65	60%	56%	58%
LH/FSH	0.787	≥1.62	78%	70%	74%
Prolactin	0.586	>39.2	58%	50%	54%
Zinc	0.561	>90.85	56%	54%	55%
Copper	0.981	≥102.3	92%	96%	94%

DISCUSSION

Polycystic ovary syndrome (PCOS) remains the most common endocrine disorder associated with infertility in women of reproductive age.[14] Its pathogenesis is complex and multifactorial, involving hormonal dysregulation, insulin resistance, and metabolic disturbances. Emerging evidence suggests that trace elements such as zinc and copper may influence metabolic pathways and oxidative stress, both of which are central to PCOS pathophysiology.[15] In the present study, age distribution was comparable between groups, minimizing potential confounding effects. Body mass index (BMI) was significantly higher among women with PCOS, consistent with previous reports confirming the strong association between obesity and PCOS.[16] Both conditions share insulin resistance as a central mechanism. Fertility rates were lower in the PCOS group, likely due to chronic anovulation and arrested follicular development, as previously described.[17] Menstrual irregularities were significantly more frequent, aligning with earlier findings that ovulatory dysfunction and progesterone deficiency are hallmark features of PCOS.[18] Hirsutism was the predominant clinical manifestation (90%), exceeding rates reported in some populations[19], possibly reflecting ethnic and regional variations.[20] Depression was more common in women with PCOS, supporting the multifactorial neuroendocrine and metabolic mechanisms proposed in earlier studies.[21] Endocrinologically, luteinizing hormone (LH) levels and LH/FSH ratio were significantly elevated in PCOS, consistent with previous investigations.[22] Although LH demonstrated moderate diagnostic performance, predictive values were lower than those reported in larger cohorts[23], likely due to sample size limitations. Follicle-stimulating hormone (FSH) showed limited predictive utility, in agreement with earlier observations that FSH is not a primary driver of PCOS pathophysiology.[24] Serum prolactin levels did not differ significantly between groups, consistent with findings suggesting that hyperprolactinemia is not a classical feature of PCOS.[25] Regarding trace elements, zinc levels were not significantly different between cases and controls and demonstrated poor diagnostic performance. This aligns with large meta-analytic data, although smaller studies have reported inconsistent findings.[26] Variations may be related to sample size, metabolic status, or insulin resistance effects.[27] Furthermore, zinc supplementation has not consistently improved hormonal profiles in PCOS.[28] Conversely, serum copper levels were significantly elevated in PCOS, with high sensitivity and specificity at the proposed cutoff. Similar elevations have been reported in observational and meta-analytic studies.[29] While some studies found no difference[30], control group selection may explain discrepancies. Elevated copper may contribute to oxidative stress and low-grade inflammation, mechanisms implicated in PCOS pathogenesis.[13] These findings suggest that copper may represent a potential biomarker in PCOS; however, further large-scale studies are warranted to confirm its clinical utility.

CONCLUSION

Zinc is poor marker of PCOS and copper level had high sensitivity and specificity to be associated with PCOS.

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