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

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ABSTRACT: Background: Multiple logistic regression analysis of several metabolic variables between polycystic ovary syndrome and control groups revealed that zinc level was the most important variable to predict polycystic ovarian syndrome. **Objective:** This study was designed to illustrate the correlation between zinc and copper levels with the biochemical changes associated with polycystic ovary syndrome. **Materials and Methods:** Twelve women with polycystic ovary syndrome and twelve healthy and normal ovulatory women were included in this study. The serum levels of luteinizing hormone, follicle stimulating hormone, progesterone, testosterone and prolactin were analyzed by enzyme linked immunosorbent assay. Serum zinc and copper was analyzed using atomic absorption spectrophotometer. Student (t) test was performed for comparison and Pearson's correlation coefficients (r) were calculated to quantify the correlation between the biochemical parameters in the study. **Results:** Both zinc and copper levels showed no significant correlation with other biochemical markers associated with polycystic ovary syndrome. The results revealed an increase in serum zinc concentration in polycystic syndrome group, while it showed no significant difference in copper levels between polycystic ovary syndrome and healthy groups. **Conclusion:** The study concluded that the rise in zinc level in polycystic ovary syndrome group might be due to the increase in oxidative stress within the body that put the antioxidant defense system in a hyperactive state in order to compensate for this stress.

INTRODUCTION: Polycystic ovary syndrome is a complex multifactorial endocrinopathy affecting a substantial population of reproductive aged women and is the most common cause of infertility [1]. Genetics and lifestyle may develop the main features of PCOS [2]. Women diagnosed with PCOS are usually presented with hyper androgenism, ovulatory dysfunction, and polycystic ovaries [3].

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Obesity and insulin resistance frequently occur in women with PCOS; increasing the risk for to metabolic complications such as type 2 diabetes, hypertension, hyperlipidemia and fatty liver [4]. The main features of PCOS, first defined by Stein and Leventhal [5] include androgenic features, menstrual dysfunction, and polycystic ovaries. PCOS diagnosis according to the national institute of health (NIH) consensus, necessitates the existence of oligo- or amenorrhea and hyperandrogenaemia without a known disorder that explain the cause of hyperandrogenaemia [6]. The Rotterdam criteria define PCOS by the presence of two of the three following features: hyperandrogenaemia, oligo- or amenorrhea and polycystic ovaries by ultrasound imaging [7].

The major therapeutic strategies in the management of PCOS are aimed to control hyperandrogenism and decrease insulin levels and insulin resistance. Insulin sensitizers (*e.g.* metformin), antiandrogenic agents (*e.g.* cyproterone) and combined oral contraceptive pills are the most common pharmacological products used in PCOS treatment [8, 9]. Metformin use in women with PCOS causes a decrease in androgen levels and improvement of hyperinsulinemia and menstrual irregularity [8].

Zinc is an essential trace element required as a structural, catalytic, and regulatory ion for many enzymes, proteins and transcriptional factors activities. As a result, zinc plays an important role in many homeostatic response of the body (*e.g.* oxidative stress) and in many biological functions (*e.g.* immune deficiency). Zinc also demonstrated multiple roles as a modulator of inflammation in cell cultures and animal model. Zinc supplementation improve inflammatory reaction in PCOS patients [10].

Copper is an essential trace element that is important to the proper functioning of organs and metabolic processes. Copper has an antioxidant action that protect cells from damage, and is also a component of many enzymes that is responsible for the release of energy from carbohydrates, fat and protein. Copper is also important for formation of red blood cells, bone and connective tissues. PCOS may result in dysregulation of systemic copper homeostasis [11]. The present study was conducted to investigate the correlation between zinc and copper levels with PCOS related biochemical parameters.

MATERIALS AND METHODS: Twelve women with an age range of 20 - 35 years; body mass index of 30.9 ± 1.6 kg/m^2 with PCOS without pharmacological treatment were included in the study. The classic criteria of chronic an ovulation and hyperandrogenism were used in the diagnosis of PCOS [8]. Ten healthy and normal ovulatory women with the same age range of PCOS women were included. The normal women were selected on the bases of having normal ovulatory menstrual cycles and not having signs and symptoms of androgenization (*e.g.* hirsutism). The study was conducted in the Specialized Center for Diabetes and Endocrinology, Al-Rusafa, Baghdad. Consent was signed by all participants and study protocol was approved by the Committee for Medical Ethics. Subjects having contraceptive pills or other hormonal medications or breastfeeding their babies were excluded from the study. Fasting blood samples were withdrawn from PCOS women at random days. For healthy women, blood samples were obtained during the follicular phase of the cycle. Blood samples used for progesterone assay were withdrawn in 21st day of the cycle (luteal phase). After preparation of serum, the levels of luteinizing hormone (LH) [12], follicle stimulating hormone (FSH) [13], progesterone, testosterone and prolactin [14] were analyzed by enzyme linked immunosorbent assay (ELIZA) according to standard procedures. Serum zinc and copper were analyzed using an atomic absorption spectrophotometer.

Data analysis was performed by GraphPad PrismV 5.01 software. All results were described as mean ± SEM. Student (t) test was performed for comparison and Pearson's correlation coefficients (r) were calculated to quantify the correlation between the biochemical parameters in the study. P <0.05 was considered statistically significant. P value with one star (*) represents significance and P value with more stars represents higher significance.

RESULTS: Fig. 1 - 8 display the mean values, standard deviation error bars and P value summaries (represented by stars) of all of the biochemical parameters in controls and PCOS patients.

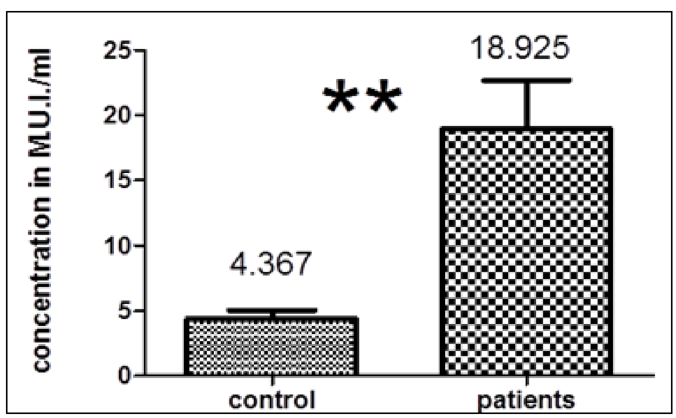

FIG. 1: PLASMA LH OF PCOS PATIENTS AND CONTROL GROUP

One star (*) represents P value less than 0.05, two stars (**) represent P value less than 0.01, three stars (***) represent P value less 0.001, no significance (ns) represents p value more than 0.05.

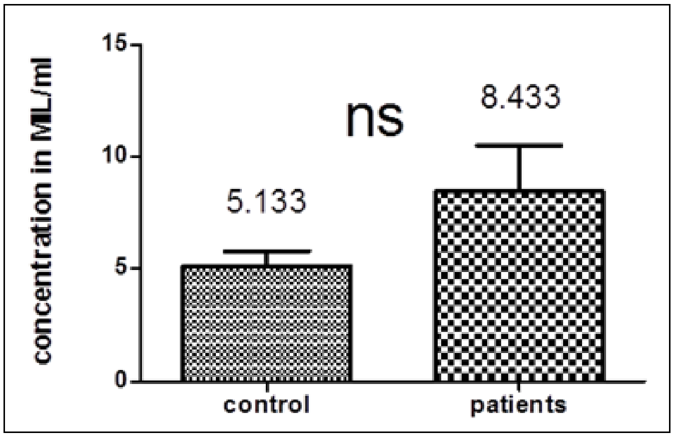

FIG. 2: PLASMA FSH OF PCOS PATIENTS AND CONTROL GROUP
One star (*) represents P value less than 0.05, two stars (**) represent P value less than 0.01, three stars (***) represent P value less 0.001, no significance (ns) represents p value more than 0.05.

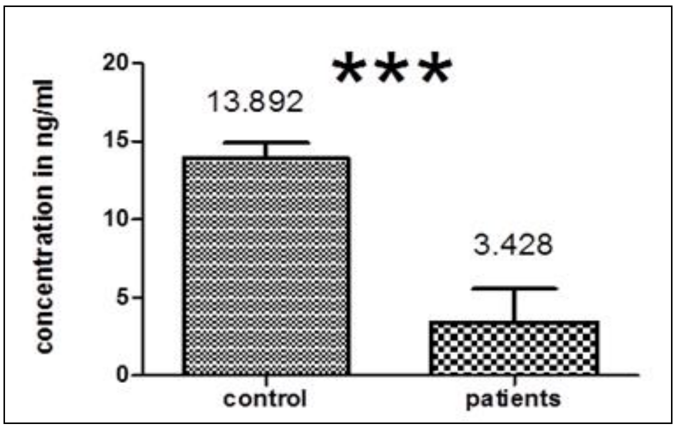

FIG. 3: PLASMA PROGESTERONE OF PCOS PATIENTS AND CONTROL GROUP
One star (*) represents P value less than 0.05, two stars (**) represent P value less than 0.01, three stars (***) represent P value less 0.001, no significance (ns) represents p value more than 0.05.

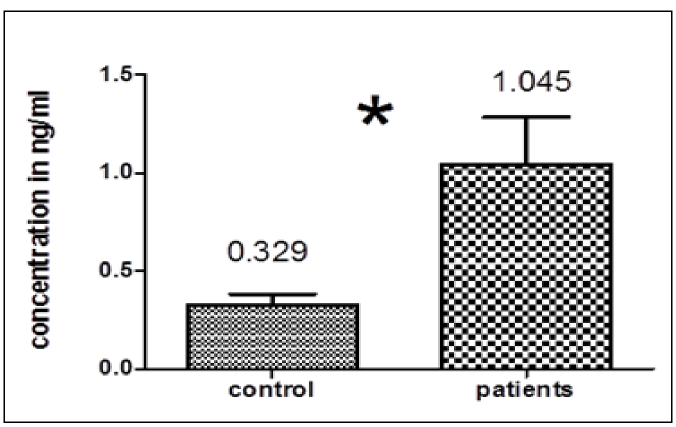

FIG. 4: PLASMA TESTOSTERONE OF PCOS PATIENTS AND CONTROL GROUP
One star (*) represents P value less than 0.05, two stars (**) represent P value less than 0.01, three stars (***) represent P value less 0.001, no significance (ns) represents p value more than 0.05.

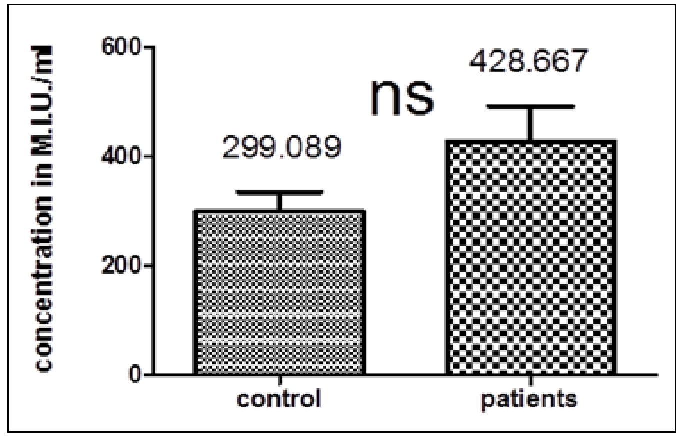

FIG. 5: PLASMA PROLACTIN OF PCOS PATIENTS AND CONTROL GROUP
One star (*) represents P value less than 0.05, two stars (**) represent P value less than 0.01, three stars (***) represent P value less 0.001, no significance (ns) represents p value more than 0.05.

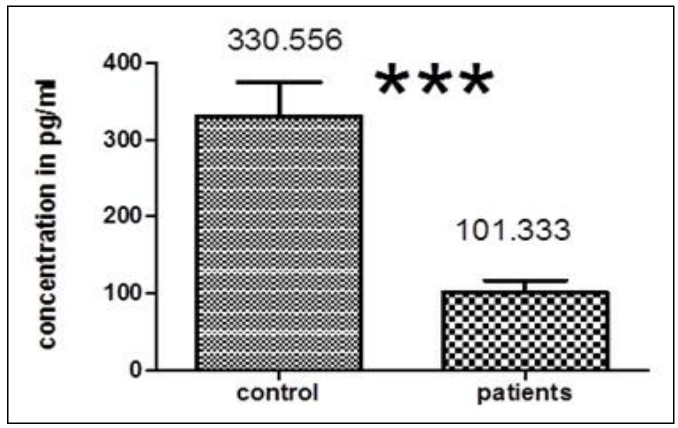

FIG. 6: PLASMA ESTRADIOL OF PCOS PATIENTS AND CONTROL GROUP
One star (*) represents P value less than 0.05, two stars (**) represent P value less than 0.01, three stars (***) represent P value less 0.001, no significance (ns) represents p value more than 0.05.

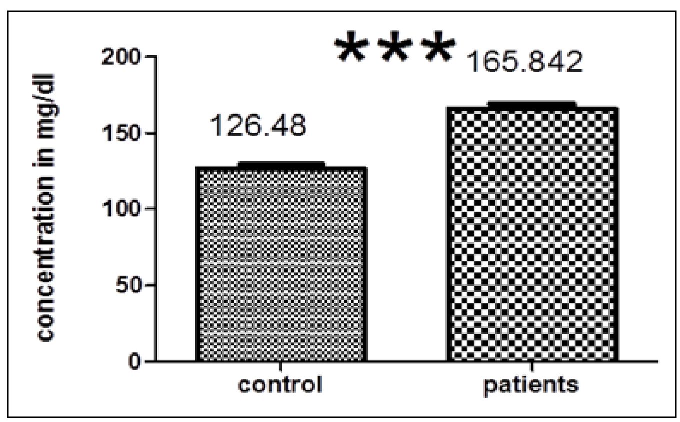

FIG. 7: PLASMA ZINC OF PCOS PATIENTS AND CONTROL GROUP
One star (*) represents P value less than 0.05, two stars (**) represent P value less than 0.01, three stars (***) represent P value less 0.001, no significance (ns) represents p value more than 0.05.

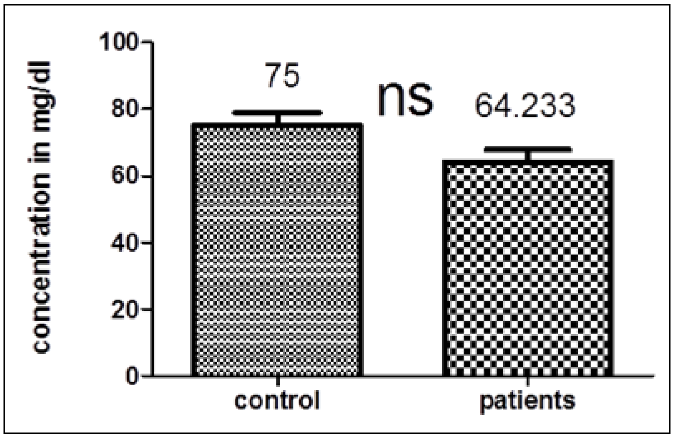

FIG. 8: PLASMA COPPER OF PCOS PATIENTS AND CONTROL GROUP
One star (*) represents P value less than 0.05, two stars (**) represent P value less than 0.01, three stars (***) represent P value less 0.001, no significance (ns) represents p value more than 0.05.

PCOS women had a significantly higher LH (P<0.01**) and testosterone (P<0.05*) levels and significantly lower progesterone (P<0.001***) and estrogen (P<0.001***) levels than the control group. Prolactin and FSH levels showed no significant difference between PCOS women and control group. PCOS patients had increased zinc levels compared to the controls which were statistically significant (P < 0.001***) while copper levels showed no significant difference between the two groups.

Table 1 shows the correlation coefficients (r) and P values of zinc and copper with biochemical parameters in PCOS group. Both zinc and copper levels showed no significant correlation with other biochemical markers associated with PCOS.

TABLE 1: CORRELATION OF ZINC AND COPPER WITH OTHER BIOCHEMICAL MARKERS IN PCOS

Parameters	Zn (mg/dl)		Cu (mg/dl)	
	r	p	r	p
LH	0.2462	0.4405	-0.5497	0.0641
FSH	0.1514	0.6385	-0.5238	0.0804
Prolactin	0.3703	0.2360	-0.07731	0.8113
Testosterone	-0.3096	0.3274	0.1775	0.5811
Progesterone	0.03062	0.9247	-0.1621	0.6148
Estradiol	-0.1052	0.7449	-0.1218	0.7062

r: Pearson's correlation coefficients; p: P (two-tailed) value

DISCUSSION: A total number of 12 patients with established diagnosis of PCOS and 12 healthy controls were selected to study the levels of biochemical parameters (LH, FSH, prolactin, testosterone, progesterone, and estradiol) and find the correlation between these biochemical parameters in PCOS patients with zinc and copper.

The higher levels of LH and testosterone and lower levels of progesterone and estrogen in PCOS women compared to control group are consistent with the Rotterdam criteria [15]. Prolactin and FSH levels showed no significant difference between PCOS women and control group which is consistent with Golzicher findings [16].

Copper is an essential trace element and co-factor for many enzymes capable of changing between the oxidized Cu^{2+} and the reduced Cu^{+} state. Cu catalyzes the synthesis of highly reactive oxygen species (ROS) that causes oxidative damage to proteins, lipids, DNA and other molecules [17]. Either Cu deficiency or excess or can lead to disease or affect the development of disease [18].

High copper levels impair thyroid function, which contributes to PCOS and infertility [19]. A recent report recorded that diabetics have elevated levels of copper and it could be that copper is in fact linked to metabolic syndrome and diabetes [1]. A meta-analysis involving three studies [18 - 20] addressing copper relationship with PCOS concluded that copper levels were found to be higher in women with PCOS than in controls [21].

The results showed that there is no correlation between copper and the rest of the biochemical parameters related to PCOS women. The study also revealed that there is no significant difference in serum copper concentration between healthy and PCOS women. Although there were three previous studies that showed higher copper levels in PCOS group than healthy group [18 - 20], a recent study [22] showed no significant difference in copper levels as well between the two groups.

PCOS women commonly have insulin resistance. Hyperglycemia may play a role in inflammation through tumor necrosis factor-α (TNF-α) production from mononuclear cells (MNCs). MNCs can produce ROS causing cellular damage and triggering nuclear factor-κB, which increases TNF-α trasncription, a well-known mediator of insulin resistance [23].

Zinc may be related to the development of polycystic ovarian syndrome and its long term metabolic complications *via* its important role in the metabolism of glucose and the synthesis, secretion, and signaling of insulin. In addition, zinc may be related to PCOS through its antioxidant effect [10, 24]. The deficiency of such a potent antioxidant such can cause an increase in oxidative damage in multiple organs, such as the heart. A deficiency in zinc also increases the risk for hypertension and atherosclerosis. Serum zinc levels have a tendency to be lower in patients with PCOS with impaired glucose tolerance [25].

The results revealed that there is no correlation between zinc and the other biochemical parameters of PCOS. Furthermore, the current study revealed an increase in serum Zn concentration in PCO group. A previous study found that serum Zn levels were significantly higher, in patients with PCOS compared with the healthy group ($p < 0.01$) [20]. This increase may be associated with disturbance of glucose metabolism represented by insulin resistance, dyslipidemia and endocrine disturbance leading to oxidative stress and finally increase Fe, and Zn. Many evidence shows that higher body zinc and iron stores are related with high risk of other insulin resistance disorder (*e.g.* high blood glucose and hyperlipidemia) [1].

A possible explanation for the increased zinc levels could be due to compensation. Antioxidant defense system being in a hyperactive state in order to compensate for the amount of oxidative stress within the body this result in consistent with other models comparing the antioxidant capacity [26]. Superoxide dismutase (SOD) activity has increased significantly in patients with PCOS compared to control. SOD is an essential antioxidant enzyme and its over - expression might be an adaptive response to oxidative stress [27]. Total antioxidant status was observed to be higher in non-obese women with PCOS [23]. Hyperandrogenism is the most common biochemical feature in PCOS women. 70 - 80% of hyperandrogenism causes is related to PCOS and is associated with high serum testosterone levels. Hyperandrogenism may manifest as acne, hirsutism, and male pattern alopecia. It is not known whether hyper-androgenemia affects antioxidant status PCOS women [28].

CONCLUSION: The present study concluded that there is no correlation between zinc and PCOS biochemical parameters. However, the results revealed significantly higher zinc concentrations in PCOS patients than control, suggesting a relationship involving oxidative stress between high zinc concentration and PCOS. Regarding copper, the evidence produced is not decisive, but suggests that additional studies are need in order to obtain new insights into PCOS.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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