The Relationship between Levels of Zinc and Copper and Insulin Resistance in Polycystic Ovary Syndrome Patients in Homs

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ABSTRACT

Objective: To investigate the association between zinc and copper levels and insulin resistance, a key pathological mechanism of Polycystic Ovary Syndrome (PCOS), and to compare these levels with those of healthy subjects in Homs.

Methods: The study included 63 female patients newly diagnosed with PCOS, prior to treatment at Al-Basil Hospital in Homs, Syria, along with 25 healthy subjects of similar age. Blood samples were collected using dry tubes for laboratory measurements of zinc, copper, glucose, and insulin hormone levels. Subsequently, the HOMA-IR and QUICKI indices were calculated.

Results: In the patients' group, serum zinc levels were significantly lower (p-value=0.000), and serum copper levels were significantly higher (p-value=0.000) compared to healthy subjects. Among patients with insulin resistance, serum zinc levels were significantly lower (p-value=0.004), and serum copper levels were significantly higher (p-value=0.000) compared to patients without insulin resistance. Patients without insulin resistance had significantly lower serum zinc levels (p-value=0.000) and significantly higher serum copper levels (p-value=0.000) compared to healthy subjects. There was a positive correlation between copper and HOMA-IR (r=0.572**, p-value=0.000), and a negative correlation between zinc and HOMA-IR (r=-0.865**, p-value=0.000).

Conclusion: The imbalance in zinc and copper levels appears to play a role in the development of PCOS, both in relation to insulin resistance and potentially as an independent factor.

Keywords: Polycystic ovary syndrome, Zinc, Copper; Insulin resistance.

1. INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a hormonal disorder that commonly affects women of reproductive age, leading to hirsutism and fertility issues primarily due to anovulation [1]. The diagnosis of PCOS is based on the Rotterdam Criteria, which necessitates the presence of two of three distinctive features: oligo or anovulation, ovarian cysts detected by ultrasound, and clinical and/or biochemical signs of hyperandrogenism [2,3]. In PCOS, there is an increase in Leuteinizing Hormone (LH) and a decrease in Follicle Stimulating Hormone (FSH), resulting in elevated levels of androstendione that remains unconverted to estrogen. The excessive androgen leads to the formation of small follicles that are incapable of maturation [4]. This syndrome presents several complications, with the most significant ones including cardiovascular issues, infertility, and mood disorders [5]. Insulin Resistance (IR) occurs when the sensitivity and response of liver, adipose, and skeletal muscle cells to normal levels of insulin are reduced. IR stands out as one of the most prominent pathological mechanisms observed in PCOS [6]. The elevated levels of insulin associated with IR increase the action of LH,

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which in turn stimulates Theca cells, ultimately resulting in increased production of androgens [7]. Zinc plays an essential role in the body, particularly in insulin secretion and sensitivity [8]. Inside pancreatic β cells, insulin pairs with two zinc ions in secretory granules to form the $ZincO_2$-Insulin6 complex, which is crucial for hormone secretion [9]. The expression of Zinc transporters (ZnTs and ZIPs) in pancreatic β cells directly influences insulin secretion [10]. Additionally, Zinc can modulate the activity of proteins in the insulin signaling pathway, ultimately enhancing glucose uptake [11]. Copper is a vital mineral essential for the proper functioning of most organisms, as it facilitates the movement of electrons within biological molecules [12]. However, an excess of copper can lead to the generation of free radicals, particularly reactive oxygen species (ROS), which in turn can cause impairments in insulin signaling pathways[13].

2. RESULTS AND DISCUSSION

Table 1 presents the demographic characteristics of the study participants. The average age in the patient group was (28.68 ± 7.22) years, and in the control group, it was (28.84 ± 7.83) years for comparison purposes. Based on HOMA-IR values, the patient group was divided into two subgroups using a cutoff value of HOMA-IR ≥ 2.5 to indicate the presence of insulin resistance (IR). Our findings revealed that (65.08%) of patients exhibited insulin resistance, while (34.92%) did not (refer to Fig. 1). The average age in the insulin-resistant patient subgroup was (29.56 ± 7.54) years, whereas in the subgroup without insulin resistance, it was (27.05 ± 6.43) years.

Table 1. Demographic data of subjects included in the study.

Demographic Characteristics	Values (mean ± SD)			
	Patients Group (63)			Control Group (25)
	Patients with IR subgroup (41)	Patients without IR subgroup (22)	Total (63)	
Age (years)	29.56 ± 7.54	27.05 ± 6.43	28.68 ± 7.22	28.84 ± 7.83
BMI (Kg/m^2)	26.13 ± 4.32	24.99 ± 4.39	25.73 ± 4.35	25.38 ± 4.90
WHR	0.80 ± 0.07	0.77 ± 0.07	0.79 ± 0.07	0.74 ± 0.06

*BMI: Body Mass Index = weight (kg)/height (m^2), IR: Insulin Resistance, WHR: Waist-Hip Ratio = waist (cm)/hip (cm)

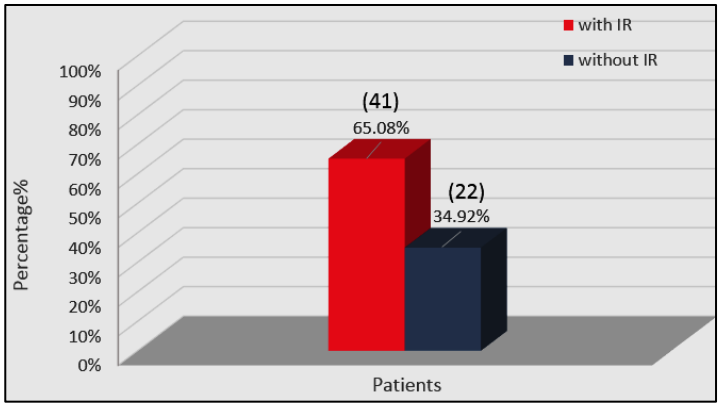

Figure 1. Distribution of patients according to the presence of IR

2.1. Distribution of study samples according to the status of zinc and copper in the serum

Table 2 displays the distribution of the study samples based on the serum levels of zinc and copper, as illustrated in Fig. 2 and Fig. 3.

Table 2. Distribution of study samples according to the status of zinc and copper in the serum.

	Zinc Deficiency	Normal Zinc	Excess Zinc	Copper Deficiency	Normal Copper	Excess Copper
Control Group (n=25)	0% (n=0)	100% (n=25)	0% (n=0)	0% (n=0)	100% (n=25)	0% (n=0)
Patients Group (n=63)	95.24% (n=60)	4.76% (n=3)	0% (n=0)	0% (n=0)	3.17% (n=2)	96.83% (n=61)

*n: number

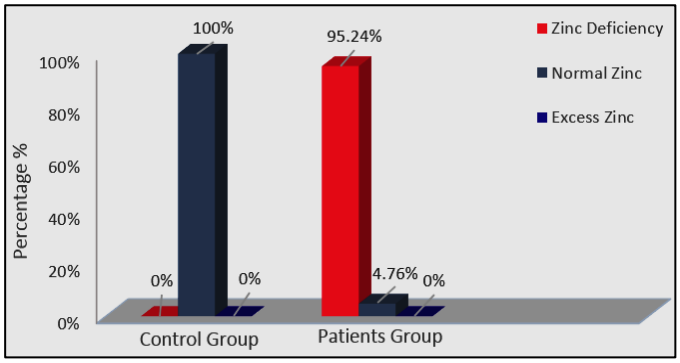

Figure 2 Distribution of study samples according to the status of zinc in the serum

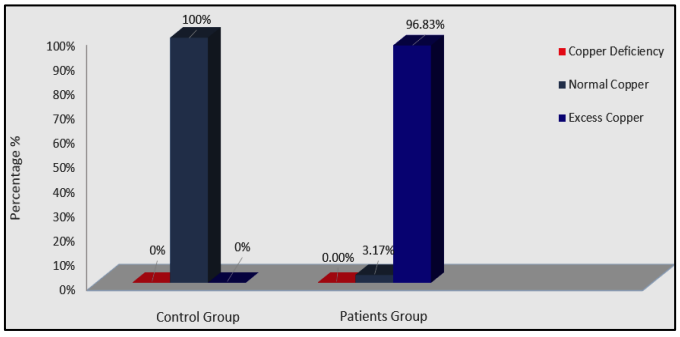

Figure 3. Distribution of study samples according to the status of copper in the serum

2.2. The comparison of the study parameter values between Control Group and Patients' Group

Table 3 presents a comparison of parameter values between the Control Group and Patients' Group. The Control Group demonstrated significant differences in serum zinc values and QUICK index, favoring this group. Conversely, significant differences were observed in serum copper values and HOMA-IR, favoring the Patients' Group.

Table 3. Comparison of the study laboratory parameters between the patient group and the healthy group.

Laboratory Parameters	Values (mean ± SD)		*p*-value
	Patients Group (n = 63)	Control Group (n = 25)	
Zinc (µg/dL)	54.14 ± 10.07	89.06 ± 11.59	0.000
Copper (µg/dL)	189.60 ± 33.26	115.13 ± 20.24	0.000
HOMA-IR [a]	2.33 ± 0.85	1.26 ± 0.70	0.000
QUICK [b]	0.34 ± 0.02	0.38 ± 0.05	0.000

a: homeostatic model assessment for insulin resistance. b: quantitative insulin sensitivity check index.

Based on the findings from Table 2 and Table 3, it was observed that patients exhibited a deficiency in zinc and an excess of copper, while these imbalances were not observed in the healthy subjects. Consequently, it can be inferred that factors related to the environment and dietary patterns significantly influence the levels of zinc and copper. It is worth noting that factors common to both healthy individuals and patients do not predominantly contribute to these deficiencies. The potential factors influencing diet- and environment-related zinc deficiencies may include: 1) The supplementation of calcium can hinder the absorption of zinc. 2) Vegetarian patients with a diet high in phytates may experience zinc deficiency, as phytates are known to bind zinc and inhibit its absorption. 3) Non-heme iron supplements may reduce zinc absorption, unlike heme iron. 4) Deficiency in the ZnT1 transporter, which is responsible for transporting zinc from intestinal cells into the bloodstream. 5) Deficiency of the Zip4 transporter, which is essential for the absorption and transportation of zinc from the intestine through epithelial cells [14]. Factors influencing copper excess deficiency related to diet and environment include: 1) Use of copper pipes for delivering drinking water to households in certain regions. 2) Preparation of food using copper pots. 3) Reduced capacity of the liver to eliminate excess copper [15]. The primary cause of zinc deficiency and copper excess is associated with polycystic ovary syndrome (PCOS) and its pathogenesis, attributed to several factors related to oxidative stress and the inflammatory response commonly observed in PCOS patients: 1) Circulating zinc binds to albumin and copper binds to ceruloplasmin in the bloodstream. The imbalance between oxidative and reductive factors in PCOS patients leads to the dissociation of these metals from their binding forms, resulting in an abundance of free copper that facilitates the transport and displacement of zinc ions into tissues, thereby reducing zinc levels [16]. 2) The inflammatory state [17] and the presence of inflammatory cytokines (IL-6, TNF-α, IL-1, IFN-gamma) regulate the production of ceruloplasmin and inhibit albumin production, consequently leading to decreased zinc levels and increased copper levels [18]. 3) In the presence of pro-inflammatory cytokines, Forkhead box protein O1 (FOXO1) enhances the antioxidant response, leading to upregulation of Zip14 in the liver, causing a decrease in zinc. Moreover, it participates in the synthesis of ceruloplasmin [19]. Our result supports the findings of several previous studies [20-22], and disagrees with a study that found no variation in the levels of these two elements;

this may be due to the small number of samples in their study (47 patients) [23].

2.3. The comparison of the study parameter values between Patients with Insulin Resistance Group (Group 1) and Patients without Insulin Resistance Group (Group 2)

Table 4 presents a comparison of study parameter values between two groups: Patients with Insulin Resistance (Group 1) and Patients without Insulin Resistance (Group 2). Significant differences were observed, with Group 2 showing higher serum zinc values and QUICK index, while Group 1 exhibited significant differences favoring copper and HOMA-IR. The greater zinc deficiency in Group 1 is attributed to its disruption of the insulin signaling pathway, a key factor in the development of insulin resistance. Zinc plays multiple roles, such as stimulating the phosphorylation of the β subunit of the insulin receptor [24], activating PI3K and AKT to promote glucose transport into cells, inhibiting PTEN (which facilitates PI3P dephosphorylation), and regulating the metabolism of glycogen and glucose conversion through the phosphorylation of GSK and inhibition of its action [25], as well as stimulating the phosphorylation of FOXO1 to regulate glucose production [26]. Similarly, excess copper in Group 1 leads to disruptions in the insulin signaling pathway. Copper's conversion from Cu+2 to Cu+1 generates reactive oxygen species (ROS), which inhibit insulin-stimulated glucose uptake and cause defective insulin signaling by phosphorylating the serine/threonine sites of the insulin receptor [27], resulting in decreased transcription of the GLUT-4 gene and reduced GLUT-4 expression, ultimately contributing to insulin resistance [28]. Our findings align with several previous studies [29,30].

Table 4. Comparison of the laboratory parameters between the Patients with IR Group and the Patients without IR Group

Laboratory Parameters	Values (mean ± SD)		*p*-value
	Patients with IR (Group1) (n=41)	Patients without IR (Group2) (n=22)	
Zinc (µg/dl)	51.52 ± 10.49	59.01 ± 7.16	0.004
Copper (µg/dl)	204.62 ± 31.92	161.59 ± 7.90	0.000
HOMA-IR	2.88 ± 0.33	1.29 ± 0.48	0.000
QUICK	0.32 ± 0.004	0.37 ± 0.02	0.000

*n= number

a: homeostatic model assessment for insulin resistance. b: quantitative insulin sensitivity check index.

(Table 5) shows Pearson test.

Table 5. Correlation coefficient in patienrs with insulin resistance group

	HOMA-IR		QUICK		Zinc		BMI		WHR	
	r	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***
Zinc	- 0.865**	0.000	0.851*	0.000	1	-	- 0.146	0.361	0.160	0.317
Copper	0.572**	0.000	- 0.574**	0.000	- 0.484**	0.001	0.174	0.275	- 0.049	0.760

In our analysis, we observed a significant negative correlation between Zn and HOMA-IR (Fig. 4) in patients with insulin resistance. Additionally, a significant positive correlation between Zn and QUICK index was identified in the same patient group (Fig. 5).

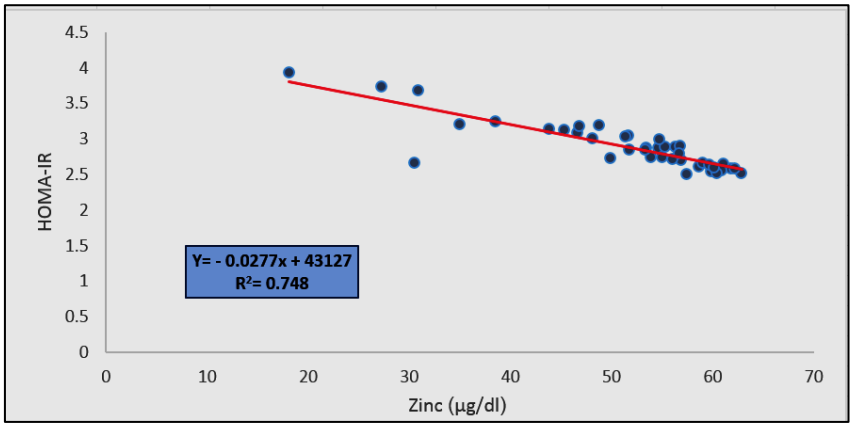

Figure 4. Correlation between serum Zn and HOMA-IR in Patients with İnsulin Resistance (r^2 = 0.784, *P*-value = 0.000)

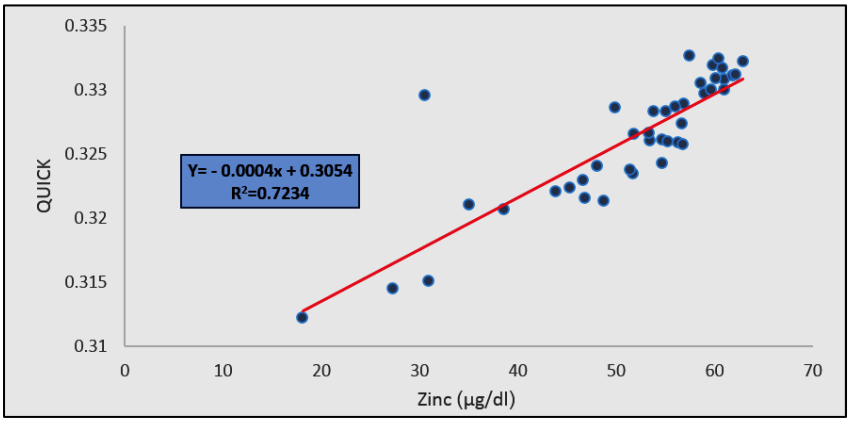

Figure 5. Correlation between serum Zn and QUICK in patients with insulin resistance (r^2 = 0.7234, *P*-value = 0.000).

Our investigation revealed a noteworthy negative correlation between Cu and QUICK (Fig. 6), as well as a significant positive correlation between Cu and HOMA-IR in patients with insulin resistance (Fig. 7).

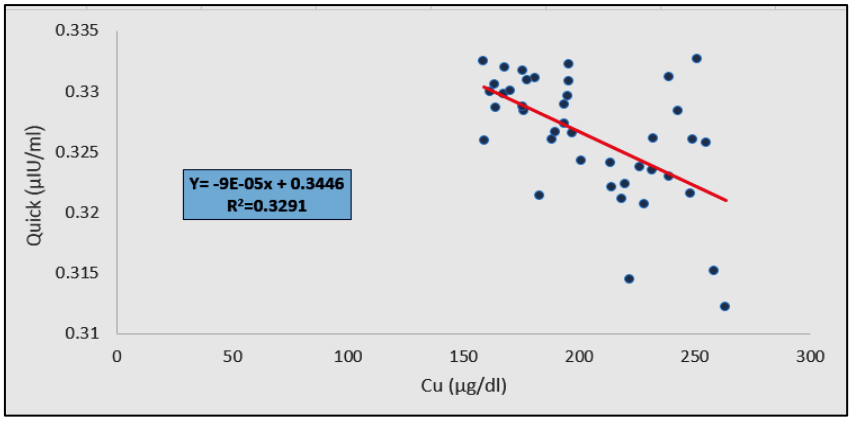

Figure 6. Correlation between serum Cu and QUICK in patients with insulin resistance (r^2 = 0.3291, *P*-value = 0.000).

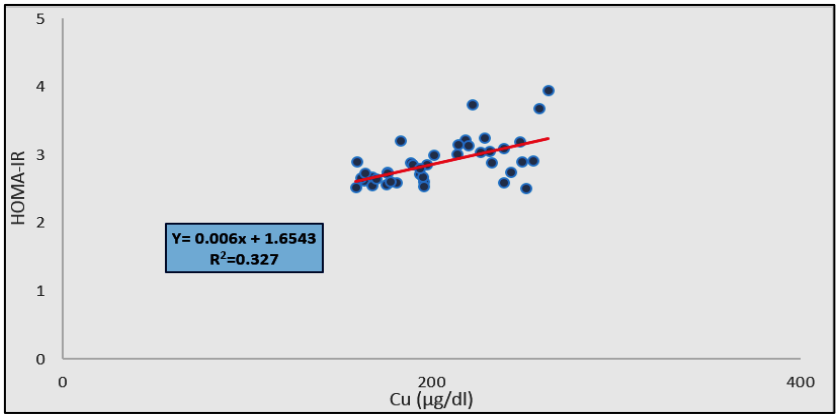

Figure 7. Correlation between serum Cu and HOMA-IR in Patients with İnsulin Resistance (r^2 = 0.327, *P*-value = 0.000).

2.4. The comparison of the study parameter values between Patients without Insulin Resistance Group and Control Group

Table 5 displays a comparison of the study parameter values between the Control Group and the Patients without Insulin Resistance Group. The study revealed significantly higher Cu levels in the Patients without Insulin Resistance Group compared to the Control Group, whereas Zn levels were markedly higher in the Control Group. These disparities in zinc and copper values between the Control Group and Patients without IR Group are attributed to their influential role in the context of PCOS independent of insulin resistance [31]. The insufficiency of zinc contributes to the pathogenesis of PCOS through causing defects in ovarian development [32], impairing the secretion of both FSH and LH [33], and acting as an anti-androgenic agent [34]. Conversely, excessive copper plays a role in the development of PCOS by affecting the secretion of adrenocorticotropic hormone and luteinizing hormone [35], reducing progesterone levels, and inhibiting the absorption of zinc, which is pertinent to the reproductive pathway [36,37].

A noteworthy observation was the significant inverse correlation identified between Cu and Zn in Patients with Insulin Resistance, as illustrated in (Fig. 8).

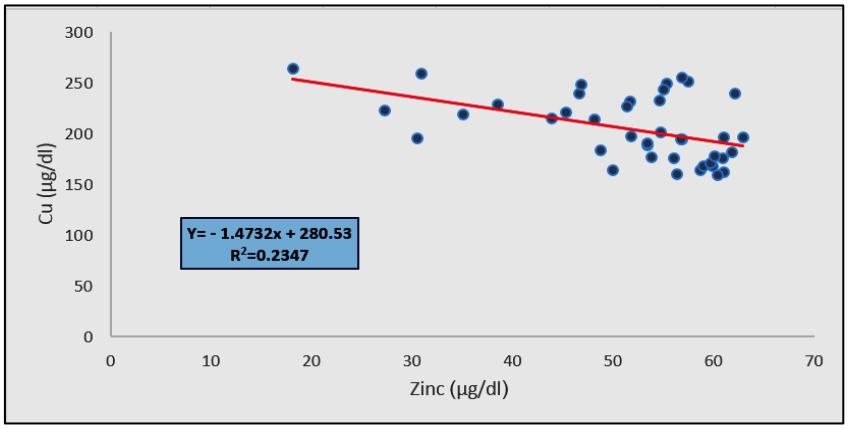

Figure 8. Correlation between serum Cu and serum Zn in patients with insulin resistance (r^2 = 0.2347, *P*-value = 0.001).

3. CONCLUSION

The study revealed a significant role for zinc and copper in the development of this syndrome, either through their association with insulin resistance or as isolated risk factors independent of insulin resistance. Consequently, we advocate for monitoring serum levels of zinc and copper and recommend maintaining them within the normal range, particularly for women with PCOS and women of childbearing age.

4. MATERIALS AND METHODS

This research was conducted at Al-Basil Hospital in Homs, Syria, spanning from June to September 2022, with each study participant providing informed written consent prior to participation.

4.1. Patients

Sixty-three (63) untreated adult female patients who were newly diagnosed with polycystic ovary syndrome were included in the study, along with 25 age-matched healthy subjects serving as the control group. The inclusion criteria stipulated that participants must be female, aged 18-43, and newly diagnosed with PCOS, without having commenced treatment. Exclusion criteria comprised individuals with diabetes, hyperprolactinemia, thyroid diseases, congenital adrenal hyperplasia, uterine cyst, breast cancer, epilepsy, Cushing's disease, and those who had used hormonal drugs, metformin, or supplements containing zinc and copper over specified time periods.

4.2. Samples

Venous blood samples were obtained from the enrolled patients after an overnight fasting period. The samples were collected from the cubital vein in sterile and dry plastic tubes and incubated in a water bath at 37°C for 30-45 minutes. Subsequently, the tubes underwent centrifugation at 3000 rpm for 10 minutes, leading to the separation of serum after clot formation. The serum was then divided into two parts, with the first part used for conducting biochemical tests (including fasting glucose, zinc, and copper) using a spectrophotometer. The second part was stored at -20°C for later measurement of fasting insulin via an ELISA device.

Insulin resistance was assessed using the homeostatic model assessment for insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI). An HOMA-IR value of ≥ 2.5 and a QUICKI value of ≤ 0.333 were considered indicative of insulin resistance. The HOMA-IR and QUICKI were calculated using their respective formulas.

$$HOMA\_IR = Glucose(mmol/L) * Insuline(mU/L)/22.5$$

$$QUICK1 = 1/\log Insulin\ (mU/mL) + \log Glucose\ \ (mg/dL)$$

4.3. Materials

In this study, various laboratory equipment was utilized, including 5 mL syringes, 5 mL dry tubes, yellow and blue micropipette heads, Eppendorf tubes, tube holders, micropipettes of different capacities, a centrifuge, and a water bath.

- Zınc monolıquıd: BIOREX / UNITED KINGDOM
- Copper (urıne/serum) colorımetrıc: BIOREX / UNITED KINGDOM
- Glucose: BIOSYSTEM / SPANISH
- Insulın ELISA: DIAMETRA / ITALY

4.4. Devices

The analysis of fasting blood glucose, zinc, and copper levels was conducted using a UV-visible spectrophotometer, while the analysis of fasting insulin hormone was performed using an ELISA device.

- ELISA: REBONIC
- U.V VIS spectrophotometer single beam, Simitronic

4.5. Statıstıcal Analysıs

Statistical analysis was performed using the Statistical

Package for the Social Sciences (SPSS) version 26.0 for Windows. Descriptive statistics were reported as mean ± standard deviation (SD). To compare means, Student's t-test was utilized. For examining binary correlations, Pearson's correlation test was employed, with the results presented as correlation coefficient (r) and P-value. Statistical significance was defined as $P < 0.05$.

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العلاقة بين مستويات الزّنك والنّحاس ومقاومة الأنسولين لدى مريضات متلازمة المبيض متعدّد الكيسات في مدينة حمص

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ملخص

الهدف: دراسة العلاقة بين مستويات الزّنك والنّحاس ومقاومة الأنسولين الّتي هي الآليّة الإمراضيّة الرّئيسيّة لمتلازمة المبيض متعدّد الكيسات (PCOS)، ومقارنة مستويات المعادن مع الأشخاص الأصحّاء في حمص.

طريقة العمل: شمل البحث 63 مريضة تم تشخيصهن حديثاً بمتلازمة المبيض متعدّد الكيسات، وقبل أن تتم معالجتهن في مستشفى الباسل في حمص، سوريا، إلى جانب 25 امرأة سليمة من نفس العمر. تمَّ الحصول على عيّنات الدّم باستخدام الأنابيب الجافّة للقيام بمقايسة مستويات الزّنك والنّحاس والغلوكوز وهرمون الأنسولين. وفي وقت لاحق، تم حساب المؤشّرات التّالية HOMA-IR وQUICK.

النّتائج: في مجموعة المريضات، كانت مستويات الزّنك في الدّم أقل بشكل ملحوظ ($p = 0.000$)، وكانت مستويات النّحاس في الدّم أعلى بشكل ملحوظ ($p = 0.000$) مقارنة بالأشخاص الأصحّاء. في المريضات اللّواتي تعانين من مقاومة الأنسولين، كانت مستويات الزّنك في الدّم أقل بشكل ملحوظ ($p = 0.004$)، وكانت مستويات النّحاس في الدّم أعلى بشكل ملحوظ ($p = 0.000$) مقارنة بالمريضات اللّواتي لا تعانين من مقاومة الأنسولين. في المريضات اللّواتي لا تعانين من مقاومة الأنسولين مقارنة بالنّساء السّليمات، كانت مستويات الزّنك في الدّم أقل بشكل ملحوظ ($p = 0.000$)، وكانت مستويات النّحاس في الدّم أعلى بشكل ملحوظ ($p = 0.000$). وُجِد ارتباط إيجابي بين النّحاس و HOMA-IR ($r=0.572^{**}$) ($p=0.000$)، وارتباط سلبي بين الزّنك و HOMA-IR ($r=-0.865^{**}$) ($p=0.000$).

الخلاصة: إنَّ خلل مستويات الزّنك والنّحاس له آثار على تطوّر متلازمة المبيض متعدّد الكيسات، سواء ترافقت مع مقاومة الأنسولين أو تواجدت بشكل مستقل عنها.

الكلمات الدالة: متلازمة المبيض متعدّد الكيسات، الزّنك، النّحاس، مقاومة الأنسولين.

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