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Association of Low Zinc Concentration and Hyperleptinemia with Overweight and Insulin Resistance in Polycystic Ovary Syndrome Women

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ABSTRACT

Background & Objective: It has been reported that low concentration of zinc in serum is associated with insulin resistance (IR), also appears to be a relationship between insulin and leptin. In this study the possibility of increased leptin concentration and zinc deficiency was evaluated. Their relationship with overweight and IR was also investigated in women with polycystic ovary syndrome (PCOS).

Materials & Methods: In this case-control study, 104 PCOS cases and 99 healthy individuals as control were included. Blood specimens were collected from participants post overnight fasting period; zinc concentrations (spectrophotometry method), leptin (ELISA method), insulin (ECLIA method), lipid profiles and glucose were measured with enzymatic method. The homeostasis model assessment (HOMA) index determined the IR level.

Results: Zinc level was 87.20 ± 11.32 µg/dl in PCOS group, and 113.68 ± 8.31µg/dl in control group. Leptin concentration was 23.06 ± 3.33 ng/mL and 19.37 ± 3.34 ng/mL, and IR was 2.37 ± 0.83 and 1.45 ± 0.74 in case and control groups, respectively (all $p<0.001$). Zinc had marked negative correlation with leptin, insulin, and IR ($p<0.001$). According to the subject, which waist circumference and body mass index (BMI) parameters were confounding factors, hyperleptinemia and zinc decrement significantly affected PCOS subjects. In contrast, only zinc decrement had an association with PCOS, after eliminating the confounding factors (OR: 0.782, $p<0.001$).

Conclusion: Zinc reduction is more effective on PCOS than hyperleptinemia. Hyperleptinemia has association with waist circumference and BMI; it can also affect PCOS. Zinc deficiency is a more effective factor than an increase in leptin concentration in women with PCOS.

Keywords: Zinc, Leptin, Insulin resistance, Overweight, Polycystic ovary syndrome

Introduction

Adipose tissue, as an endocrine gland, affects metabolic processes by secreting adipokines. Leptin hormone with polypeptide structure is one of these adipokines which plays an important role in several physiological functions such as immunity and reproduction and energy homeostasis, and maintenance of normal body weight (1-3). Some studies have shown that leptin expression is enhanced by insulin, while leptin suppresses insulin secretion from pancreatic β cells. In fact, there appears to be a two-way relationship between β cells and adipose tissue (4, 5). Normal levels of zinc in humans are vital for the suitable functioning of physiological and metabolic processes, lessening zinc levels, particularly in obesity-related processes, has negative impacts (6). Zinc acts as an anti-inflammatory and antioxidant nutrient by contr-olling transcription variables that are vital for lipid amalgamation and oxidation. Taking zinc supplements in hefty ladies plays a vital part in controlling weight and ensuring against the chance of cardiovascular malady (7). Zinc supplementation may be a valuable technique for the treatment of the metabolic dysfunction related with obesity (8). Polycystic ovary syndrome (PCOS) is introduced as the main endocrine disorder in women (prevalence 9-18%) at regenerative age. Obesity and the distribution of abdominal fat in women with PCOS in the middle years of fertility increase the chances of deve-

loping type 2 diabetes compared to the normal group (9). Hypertension and insulin resistance (IR) are observed as it were in obese women with PCOS, which puts them at chance for low-grade inflammation and cardiovascular disease (10). IR is found in 50-70% of PCOS involved women; it is presently acknowledged as a significant risk factor for metabolic syndrome advancement in cited individuals (11). Low BMI-independent adiponectin concentrations and IR with compensatory hyperinsulinemia were detailed in PCOS (12). About 80% of PCOS women have obesity and an additional load of IR is forced on them due to the nearness of abundance fat in them (13, 14). Since there are inadequately thinks about on the concentration of zinc and leptin and their relationship with overweight and affront resistance in PCOS, within the show consider, serum zinc and leptin levels were measured; the relationship with overweight and insulin resistance were also inspected.

Materials and Methods

Subjects: 203 women among 18 and 38 years involving 104 recently analyzed PCOS women and 99 healthy individuals as control were selected at current research. The considerable studied individuals were outpatients in the Gynecological Clinic Fatemieh Hospital of Hamadan College of therapeutic sciences from April to October 2020. Based on Rotterdam criteria, presence of the two out of three following features is considered as PCOS, clinical and/or biochemical signs of hyperandrogenism, polycystic ovaries and oligo-or anovulation (15). Patients by secondary causes of PCOS as described below were excluded: Cushing syndrome, prolactinoma, innate adrenal hyperplasia, virilizing ovarian and adrenal tumors.

Controls were selected from similar population from point of socioeconomic characteristics; they were coordinated for age and body mass index (BMI) by the cases. Whole control individuals had normal ovulating cycles; no hyperandrogenism signs were observed. There was not any systemic sicknesses or medication consumption which might affect reproductive system or physiology. The ethics committee of Hamadan University of Medical Sciences (ethics committee code: IR.UMSHA.REC-.1399.039) was confirmed the present research. The research purposes were explained to whole participants; they signed the informed consent. The participants did not pay any money for biochemical tests performance; the test results were also reported to them.

Measurements:

Participants weight was measured to the closest 0.1kg by a balanced-beam scale. Moreover, and height was also measured with a stadiometer to the nearest 0.5 cm, while participants had light clothes. BMI is always calculated based on the following formula: weight/(height^2) equation; it was computed based on the cited formula.

Waist circumferences is defined as the distance between the least rib and the iliac crest in umbilicus level; it was measured duplicity by an adaptable tape. Blood tests were gathered during the days 3- 6 of unconstrained menstrual cycle in all women, after 12 hours fasting at 08-09 Am. The primary levels of FSH, LH, leptin, serum glucose, zinc, lipid profile and insulin were measured. The homeostasis model assessment index (HOMA)-B were calculated based on the following formula for β-cell function: (fasting plasma insulin (mU/l) ×20 /fasting plasma glucose (mmol/l) – 3.5); HOMA-IR was also calculated for IR (fasting plasma insulin (mU/l) ×fasting plasma glucose (mmol/l)/22.5). IR was defined as HOMA index ≥2.1 (16).

Lipid profile and serum glucose were assessed with enzymatic method (Pars Azmoon, IRAN). Insulin, LH and FSH were computed with electrochemiluminescenc immunoassay (ECLIA) via commercial kits (DRG, Germany); leptin was also assessed via ELISA (Biovendor, Czech Republic, no. RD191023100). Efficiency of test was 0.5 ng/mL, and the measurable range of kit was 1–150 ng/mL. Serum zinc was assessed via spectrophotometer Biorex symptomatic unit (BXC0462, UK).

Statistical Analysis:

Data were recognized as mean±SD. Statistical analysis was handled by SPSS version 20. Student's t-test, Mann-Whitney test and ANOVA test were also performed to compare the groups. Bivariate correlation survey (Spearman coefficient calculation) was used to evaluate the relation of leptin, zinc and insulin to each parameter. To assess the autonomous impact of low zinc and hyperleptinemia on PCOS after changing conditions for confounding variables, Multiple logistic regression analyse was used. $p<0.05$ was considered as statistical significance level.

Results

The anthropometric, biochemical, and hormonal characteristics of studied women were computed; their statistical significance are noted in Table1. As can be seen, the studied women were matched in terms of age and BMI, respectively (p=0.698, p=0.412). The results display the mean value for zinc, leptin and insulin is difference in both groups (p<0.001).

Table 1. Biochemical and clinical findings of PCOS subjects and control group (mean ±SD).

Variable	Control group (n = 99)	Case group (n = 104)	p value
Age	26.13 ± 5.01	25.90 ± 4.13	0.698
BMI(Kg/m^2)	26.50 ± 4.10	26.95 ± 3.49	0.412
Waist(cm)	86.44 ± 10.95	91.57 ± 11.12	0.001

Variable	Control group (n = 99)	Case group (n = 104)	p value
FBS(mg/dl)	82.75 ± 7.18	84.03 ± 5.82	0.166
TC(mg/dl)	162.99 ± 34.26	172.63 ± 33.85	0.045
TG(mg/dl)	124.18 ± 22.96	151.21 ± 58.34	0.002
LDL(mg/dl)	92.76 ± 22.53	101.34 ± 22.04	0.007
HDL(mg/dl)	48.77 ± 9.36	47.33 ± 9.34	0.27
LH/FSH	1.37 ± 0.91	3.50 ± 0.26	< 0.001
Zinc(µg/dl)	113.68 ± 8.31	87.20 ± 11.32	< 0.001
leptin(ng/ml)	19.37 ± 3.34	23.06 ± 3.43	< 0.001
Insulin(µU/ml)	7.02 ± 3.29	11.41 ± 3.84	< 0.001
HOMA-IR	1.45 ± 0.74	2.37 ± 0.83	< 0.001

BMI: body mass index; FBS: fasting Blood Sugar; TC: total cholesterol, TG: triglyceride; LDL: low HDL: high density lipoprotein; LH/ FSH: the ratio of luteinizing hormone to follicle-stimulating hormone; HOMA index: homeostasis model assessment index

Although serum zinc levels and leptin concentration of both groups had a statistically significant difference; after dividing the groups based on BMI into two subgroups, significant difference was only observed in mean zinc in PCOS group (Table2).

Table2. Differences in Zinc, leptin and other parameters based on BMI, in PCOS and control groups

Parameter	Control group (n = 99)			Case group (n = 104)		
	BMI<25 (39)	BMI≥25 (60)	p value	BMI<25 (27)	BMI≥25 (77)	p value
Waist(cm)	79.92 ± 7.79	90.68 ±10.66	<0.001	80.00 ± 6.08	95.62 ± 9.52	<0.001
Insulin(µU/ml)	6.23 ± 2.52	7.54 ± 3.64	0.037	9.06 ± 3.24	12.23 ± 3.72	<0.001
HOMA-IR	1.26 ± 0.56	1.58 ± 0.81	0.019	1.82 ± 0.66	2.57 ± 0.79	<0.001
Zinc(µg/dl)	117.79 ± 5.45	111.00 ± 8.78	<0.001	89.83 ± 12.92	86.29 ± 10.64	0.164
Leptin(ng/ ml)	17.46 ± 2.31	20.62 ± 3.48	<0.001	20.70 ± 2.78	23.88 ± 3.12	<0.001

BMI: body mass index; HOMA index: homeostasis model assessment index

However, after dividing the groups based on HOMA index, the mean zinc and leptin in PCOS group was significantly different in women with IR (Table3).

Table3. Zinc, leptin and other parameters in PCOS and control subjects based on HOMA-IR

Parameter	Control group (n = 99)			Case group (n = 104)		
	HOMA-IR<2.1 (87)	HOMA-IR≥2.1 (15)	p value	HOMA-IR<2.1 (41)	HOMA-IR≥2.1 (63)	p value
Waist(cm)	79.92 ± 7.79	85.71 ± 10.83	0.169	86.12 ±10.44	95.11 ±10.13	<0.001
BMI(Kg/m2)	26.17 ± 3.66	26.51 ± 4.91	0.962	25.38 ± 3.09	27.79 ± 3.40	<0.001
Insulin(µU/ml)	6.12 ± 2.13	13.43 ± 3.50	0.962	8.00 ± 1.52	13.64 ± 3.21	<0.001
Zinc(µg/dl)	113.37 ± 8.62	108.09 ± 17.07	0.580	90.69 ± 11.76	84.94 ± 10.50	0.011
Leptin(ng/ ml)	19.16 ± 3.30	20.60 ± 3.73	0.129	22.00 ± 3.38	23.75 ± 3.14	0.011

BMI: body mass index; HOMA index: homeostasis model assessment index

According to logistic regression analysis, PCOS negatively affects zinc level independent of BMI and waist circumference. PCOS occurrence risk was higher than individuals with lower levels of zinc (OR: 0.770, p<0.001). Risk estimation significantly remained positive after leptin adjustment (OR: 0.767, p<0.001). In confounders' presence (waist circumference and BMI), leptin and zinc are associated with a higher risk of PCOS. Since by removing the above factors, only serum zinc levels are associated with PCOS (per unit decrease in zinc concentration increases the chance of developing PCOS 0.782 times), it can be concluded that zinc deficiency compared to other factors, higher affects the disease. A significant correlation was found between insulin with zinc and leptin, respectively (r: −0.575, p<0.001 and r: 0.473, p<0.001) Fig1, but after adjustment based on the group, no correlation was seen between zinc and insulin in the controls (p>0.5), reducing zinc in the presence of PCOS can increase Insulin and consequent IR in PCOS women. Zinc was also negatively correlated to leptin (r:-0.565, p<0.001) Fig1.

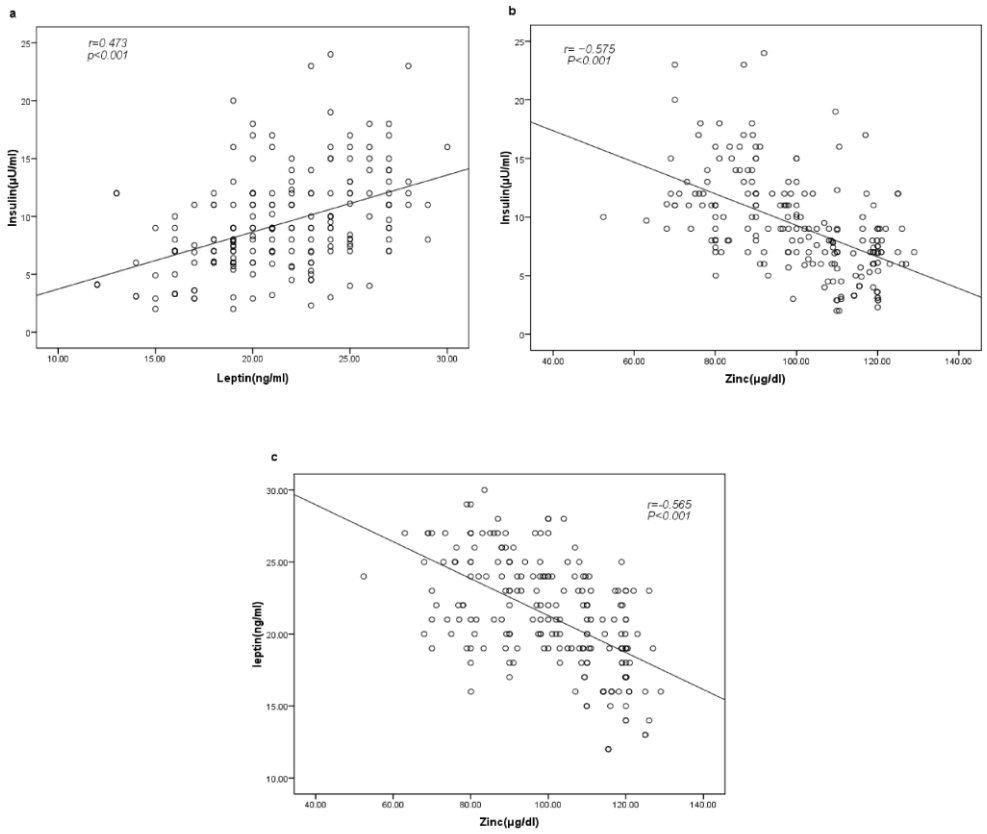

Figure 1. Correlation of insulin and leptin levels (a), Correlation of insulin and zinc levels (b), Correlation of leptin and zinc levels(c), Spearman's correlation coefficient (r) was used to examine the relationship between the variables.

Discussion

This research identified zinc concentrations to be altogether lower in women with PCOS autonomous to BMI. Besides, a converse relationship was found among zinc and leptin levels. This research about indicated the relationship among low concentrations of zinc in PCOS subordinate to IR and free to BMI. We found that the association of hyperleptinemia with PCOS is zinc subordinate. To the best of our information, it is often the primary research in which there's a possible role for zinc and leptin with IR and BMI in a critical test of women with and without PCOS Controls were inspected. In this research, an important diminish in serum zinc levels was seen within the cases in comparison to the controls. Diminished serum zinc levels in women with PCOS have nearly mentioned **(17)**. In our reseach, a direct correlation was watched between low zinc concentrations and expanded insulin resistance in women with PCOS. These findings are steady with past researches, in spite of the fact that the cut-off of IR was distinctive within the two researches, both researches appeared an increment in insulin resistance in women with PCOS. In our research, after partitioning the groups into two subgroups based on BMI, the results appeared that the rate of IR in both groups in overweight and obsess individuals (BMI ≤ 25) was altogether higher than typical weight within the same group. In any case, the results of their research did not appear a noteworthy contrast in BMI in IR women with PCOS with non-IR PCOS **(18)**. In spite of the fact that the current research found a diminish in

serum zinc levels within the case group, a research in Turkey has expressed, that mean levels of zinc in PCOS women were not significantly different from control group, which negated our findings. This contrast is likely due to the number of tests, the strategy of estimation or racial contrasts. Hence, IR in both researches was essentially higher in PCOS women than control group **(19)**. Moreover, the findings of Aliyev et al. consider in Turkey appeared that serum levels of zinc in PCOS group was not measurably critical with the control group. In this research, due to the anti-androgenic impacts of zinc, 4 groups (hirsutism, idiopathic causes, PCOS and control group) were examined, but no measurably noteworthy contrast was watched among the groups in terms of serum zinc levels, which negates the comes about of the current research. The reason for this contrast might be the littler number of tests in that consider. Furthermore, the groups were not coordinated in terms of BMI. Due to these contrasts within the plan of the two findings, the contrast in comes about can be clarified. Opposite to our researches, in both studies in Turkey, serum level of zinc in PCOS involved women and controls was not essentially distinctive (20). Taher et al. detailed mean zinc level in PCOS women was altogether lower than women without PCOS, which is reliable with the current research. Moreover, the IR rate in PCOS women, in hefty and overweight women was higher than ordinary weight women within the same group. Moreover, in both researches, after separating the groups based on BMI index (obese and overweight - typical weight), no significant difference was watched within the sum of zinc in any of the groups **(21)**. In spite of the fact that in our research the decrease in zinc concentration within the persistent group was autonomous of BMI, but within the control group, the sum of zinc in overweight and obese individuals was altogether lower. Rios-Lugo et al. illustrated diminished serum zinc levels in overweight and corpulent individuals **(6)**. In line with previous studies, mean leptin levels of PCOS women were significantly higher than controls, in the present study **(22, 23)**. Although there was no increase in leptin levels, insulin levels were elevated in PCOS women. However, in the present study after dividing the patient and normal groups into two subgroups based on BMI index (normal weight subgroup and obese subgroup), serum level of leptin in obese women was high **(24)**. According to our study a significant correlation was detected between leptin and BMI parameter in PCOS women. Our study is in line with studies which found that increased leptin levels directly correlate with the BMI **(22, 23, 25)**. Although, according to a study, in women with PCOS there was no increase in leptin levels but insulin levels were elevated **(26)**. On the other hand ,other studies reported a strong positive correlation between leptin and IR **(24, 27, 28)**. Based on previous studies findings, IR is known as a risk factor for PCOS diagnosis. In the present study, IR was higher in PCOS women; it significantly increased in obese women (**29**). As in a previous study, their findings showed that IR in women with PCOS was significantly higher than in normal women **(12, 30)**. This study showed insulin secretion index (HOMA-B) was higher in PCOS subjects; it was independent of BMI.

Conclusion

In conclusion, the current study results are matched with previous data supporting a link of increased IR with PCOS. Furthermore, for the first time our results note, that low concentration of serum zinc is probably connected to PCOS; it is also IR dependent. Also, hyperleptinemia was dependent on IR and BMI in PCOS. Although more studies are needed in this regard, but it is possible that taking zinc supplements and losing weight along with the main treatment can be effect in reducing IR and leptin levels in PCOS cases.

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Conflict of Interest

Authors declare that they have no conflict of interest.

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