Original Article

Serum Zinc Levels in Women with Polycystic Ovarian Syndrome are Lower as Compared to Those without Polycystic Ovarian Syndrome: A Cohort Study

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Abstract

Background: Zinc is an essential micronutrient, a vital stabiliser and a cofactor in many enzymes such as superoxide dismutase and phospholipase C and also acts as an antioxidant by protecting the sulfhydryl groups of different proteins and enzymes against free radicals. It is unclear if serum zinc levels are correlated with polycystic ovary syndrome (PCOS) and its pathophysiology, although relation between diabetes and insulin resistance has been established. **Aims:** This study aimed to investigate circulating serum zinc levels in PCOS subjects compared with non-PCOS subjects. **Settings and Design:** In this cohort study, PCOS subjects were compared with normal subjects aged between 18 and 35. **Materials and Methods:** All the included subjects underwent measurement of anthropometric parameters, fasting insulin, luteinising hormone, follicle-stimulating hormone, thyroid-stimulating hormone, prolactin, progesterone, oestrogen and serum zinc levels. These values were taken on days 2–5 of the menstrual cycle. **Statistical Analysis Used:** Univariate analysis and linear regression were performed for serum zinc levels and fasting insulin levels in PCOS subjects and non-PCOS subjects using SPSS (version 21) and Microsoft Excel (2019). **Results:** Serum zinc levels in the PCOS group were lower than in the control group ($P = 0.012$). Fasting insulin levels in the PCOS group were higher than in non-PCOS subjects ($P = 0.001$). We found a negative correlation between zinc and fasting insulin ($r = -0.580$, $P < 0.0001$) in the normal group and ($r = -0.332$, $P = 0.019$) in the PCOS group. A positive correlation was found between body mass index (BMI) and fasting insulin levels in both the PCOS group ($r = 0.227$, $P = 0.112$) and normals ($r = 0.612$, $P < 0.0001$). A negative statistically significant correlation between BMI and zinc in both the PCOS group ($r = -0.378$, $P = 0.007$) and the non-PCOS group ($r = -0.7452$, $P < 0.0001$) was seen. **Conclusion:** The data suggest that serum zinc levels were found to be lower in PCOS subjects as compared to normal controls and evaluation of these levels may indicate that zinc has a vital role in PCOS pathophysiology.

Keywords: *Fasting insulin, polycystic ovarian syndrome, serum zinc*

Introduction

Polycystic ovary syndrome (PCOS) is a disorder of chronic abnormal ovarian function affecting at least 10%–15% of women of reproductive age, and is defined by the Rotterdam consensus criteria.[1] The symptoms of PCOS include menstrual disturbances (irregular

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menses, oligo- or amenorrhoea), anovulatory infertility, hirsutism, persistent acne androgenetic alopecia, along with obesity, also acting as an exacerbating factor.[2]

The glycaemic profile is often affected, as is evident by the increase in fasting insulin, which is often coupled with an impaired glucose tolerance, reflecting the key role of insulin resistance in the pathophysiology of PCOS.[3] Insulin resistance and higher fasting serum insulin levels (>30 μU/dL) are common amongst obese women and some slender women with PCOS. In addition, due to their heightened risk of insulin resistance at lower body mass index (BMIs) compared to Caucasians, it is recommended that South Asian women undergo glucose tolerance assessment if their BMI exceeds 25 kg/m^2.[4]

Although the exact aetiology of PCOS is unclear due to multifactorial causation, recent reports have indicated an association between PCOS and the serum levels of trace elements such as zinc and oxidative stress.[5] Zinc is a multivalent cation that has a vital role acting as a stabiliser, cofactor in many enzymes such as superoxide dismutase and phospholipase C. It also acts as an antioxidant by protecting different proteins and enzymes that contain the sulfhydryl groups, against free radicals.[6] Zinc has other uses that include use in diarrhoea, slowing the progression of age-related macular degeneration, upper respiratory infection and its deficiency causes impaired wound healing.[7] Zinc has been observed to exhibit insulin-like effects, potentially attributed to its ability to inhibit glycogen synthase kinase 3, a crucial enzyme, that is involved in glycogen regulation.[8] Moreover, zinc plays a vital role in pancreatic β-cell function by facilitating the crystallisation, storage and processing of insulin through the action of pancreatic transporter ZnT8, which transports zinc into the insulin-secreting cells,[9] as shown in Figure 1.

Insulin is bound as a solid hexamer around Zn^{2+} in β-cells of the pancreatic islets.[10] As shown in Figure 1, Insulin and C-peptide are secreted in equal amounts, though their concentrations in the bloodstream may differ. It is suggested that the active form of C-peptide binds to zinc. Furthermore, research indicates that insulin binds more strongly to isolated liver membranes when zinc is present, leading to less degradation.[11] The protein ZnT-8 helps transport zinc into vesicles, where insulin forms a hexamer around zinc. Additional zinc is added to the vesicle, which then releases insulin, C-peptide and zinc into the β-cell on reaching its surface.[12]

Studies have indicated that zinc supplementation effectively enhances glucose regulation and mitigates insulin resistance in PCOS patients.[13] A significant improvement in lipid parameters has been observed after the administration of zinc supplements when compared with placebo.[13]

Previous studies have postulated a link between insulin resistance and zinc deficiency in PCOS women.[5] Thus, this study aims to assess serum zinc levels and insulin levels in patients with PCOS and may as well explain the link between zinc status and PCOS state in these subjects.

Materials and Methods

Study subjects

This study recruited 50 women with PCOS, as defined by the Rotterdam's criteria.[14] 50 non-PCOS women were taken for comparison.

The calculation of sample size was done using a previous study done by Kanafchian *et al*.[15] that has calculated the effect of serum zinc levels on PCOS subjects. Formula used:

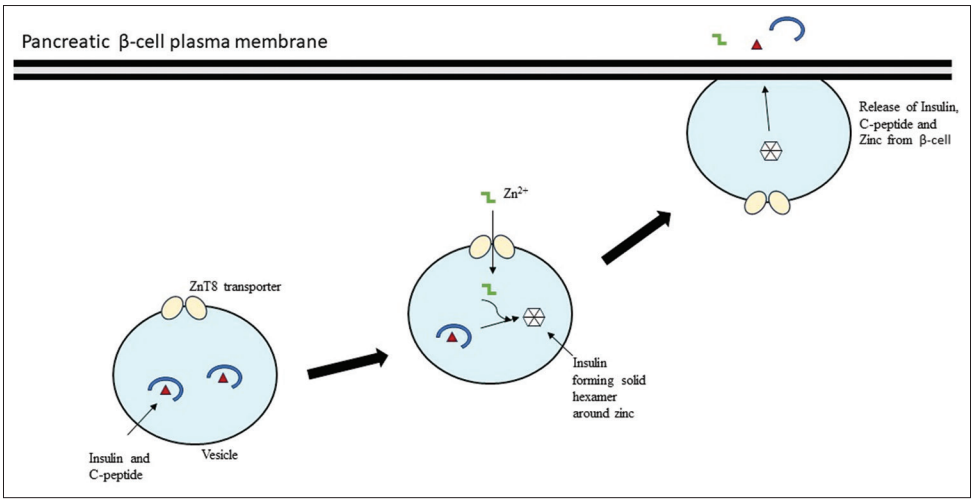

Figure 1: Insulin secretion and role of ZnT-8 and zinc ions (Zn^{2+}) in the pancreatic beta cell. (Original art created by authors in Microsoft PowerPoint)

$$n = 2\ ([\sigma_1 Z_{a/2}\,(2T) + Z_{1-\beta}]/[\mu_A - \mu_B])^2$$

where T = number of pairwise comparisons. The number of subjects to be taken in the sample came to be around (n = 45), but because of the loss to follow-up of the subjects or non-responders we added a 10% error and took (n = 50) in each group.

These subjects were further subdivided according to BMI, with equal numbers in each subgroup in both PCOS and non-PCOS groups, as shown in Table 1.

The inclusion criteria for the PCOS group were women aged 18–35 years and fulfilling the Rotterdam's criteria (two out of three): Oligo or anovulation, ultrasonographic picture of polycystic ovaries (12 subcortical follicles, 2–9 mm in diameter with dense stroma and/or increased ovarian volume (more than 10 cm^3) and clinical or biochemical evidence of hyperandrogenism.

Inclusion criteria for the control group were women aged 18–35 years old not having PCOS and coming to the outpatient department for other minor ailments. Women with thyroid disorder, deranged prolactin, type 2 diabetes or other metabolic conditions, pelvic inflammatory diseases, and women already on supplements prior to evaluation, were excluded from the study.

Ethical policy and institutional review board statement

The study protocol was approved by the Institutional Ethics Committee vide letter no LHMC/IEC/Thesis/2019/29 on 28th October 2019. The procedures follow the guidelines that are laid down in the Declaration of Helsinki 2013. A signed written informed consent was obtained from all the participants before recruitment.

Methodology

Women diagnosed with PCOS fulfilling inclusion criteria were divided into three groups as BMI <23 kg/m^2 (normal), BMI 23–25 kg/m^2 (overweight) and BMI >25 kg/m^2 (obese) as per South Asian BMI standards.[16] Women without PCOS were taken for comparison in the same subgroup as the PCOS group. All women were assessed clinically and by ultrasonography. Fasting blood samples were collected on days 2–5 of the menstrual cycle.

Table 1: Subgrouping in polycystic ovary syndrome and control group

BMI (kg/m^2)	<23	23–24.99	>25
PCOS (number of subjects)	14	13	23
Non-PCOS (number of subjects)	14	13	23

BMI=Body mass index, PCOS=Polycystic ovary syndrome

Blood was collected in a sterile tube (5 mL) labelled with the identification number and the collection date. Whole blood was stored at 4°C–8°C for up to 24 h before the serum was separated, and was not allowed to freeze. Whole blood was then centrifuged at ×1000 gravitational units (g) for 10 min to separate the serum from whole blood. The serum was carefully removed with a fine-bore pipette avoiding extraction of red cells, and then transferred to a sterile vial labelled with the patient's identifier, specimen type and date of collection. Then, the serum zinc levels were measured by fully automated clinical chemistry Autoanalyzer AU 680 (Beckman Coulter Inc., USA) based on the principle of colorimetry/photometry. hormonal assays for luteinising hormone (LH), follicle-stimulating hormone (FSH), testosterone, insulin were done by chemiluminescence assay. Zinc levels were statistically compared between the groups and correlated with insulin levels and BMI in both groups.

Statistical analysis

The data were expressed as mean ± standard deviation (SD) and total range. The Kolmogorov–Smirnov test was used to test the normal distribution of continuous variables. Statistical comparison was carried out using Student's t-test wherever appropriate. Linear regression analysis (Pearson's correlation method) was used to analyse independent variables predicting the correlation between zinc, BMI and fasting insulin levels. Data were analysed with SPSS 22 (SPSS, Chicago, USA). A two-sided $P < 0.05$ was considered statistically significant.

Results

Anthropometric characteristics and hormonal levels of subjects

As shown in Table 2, there were no statistically significant differences between the two groups in terms of age, weight, height and BMI. Furthermore, there were statistically comparable differences between waist circumference (WC), hip circumference (HC), waist/hip ratio (WHR) and age at onset of menarche. The PCOS group had higher values of WC, HC and WHR. However, the PCOS group had higher values of thyroid stimulating hormone, LH, oestradiol, testosterone and fasting blood sugar (FBS), while had lower progesterone levels.

Zinc and fasting insulin levels in the study groups

As shown in Table 3, the PCOS group had lower zinc levels in between the two groups. The control group had lower mean fasting insulin levels when compared with the PCOS group.

Correlation analysis of variables

As shown in Figure 2, the serum zinc levels were negatively correlated with BMI in the PCOS group with $r = -0.378$ and $P = 0.007$, and the serum zinc levels were also strongly negatively correlated with BMI in the non-PCOS group with $r = -0.7452$ and $P = 0.0001$. The fasting insulin levels were positively correlated with BMI in the non-PCOS group with $r = 0.6122$ and $P = 0.0001$. Whereas the serum zinc levels were negatively correlated with fasting insulin levels in the PCOS group with $r = -0.332$ and $P = 0.019$ and strongly negatively correlated in the control group with $r = -0.5808$ and $P = 0.0001$.

Discussion

The presence of significant differences in serum zinc levels between patients with PCOS and healthy subjects has been found; however, there was inconsistent BMI subgrouping in various studies.[5] The mean BMI (kg/m²) in our study was found in PCOS group as (25.82 ± 4.74) kg/m² and in non-PCOS subjects as (25.64 ± 3.95) kg/m² and also the non-PCOS were BMI matched with the subjects. Similarly, in the Indian studies by Ganie *et al*. in 2016[17] and Jena *et al*. in 2017,[18] the mean BMI amongst PCOS subjects was not significantly different from non-PCOS subjects. In the study by Macut *et al*.[19] in 2013, the reported BMI (kg/m²) was (22.99 ± 4.57) in the PCOS group and (21.62 ± 3.88) in the non-PCOS group. Other studies by Wiltgen *et al*.[20] and Mario *et al*.[21] also reported similar BMI and the difference in mean BMI of cases and controls were not significant. Jena *et al*.[18] Cuttack, India reported 38 (65%) out of 58 women with PCOS and 23 (57%) out of 40 non-PCOS subjects had BMI >25 kg/m². In a study by Wanderley *et al*.,[22] obesity (≥30) was diagnosed in 56.62% of the study population and overweight (25–29.9) in 24.09% of the patients.

In our study, we found 50% of the PCOS subjects and 20% of non-PCOS subjects had WC ≥88 cm, which is regarded as one of the criteria of metabolic syndrome.[23] The mean WHR was (0.87 ± 0.05) cm in PCOS subjects and (0.84 ± 0.03) cm in non-PCOS subjects. A WHR cut-off of 0.85 was taken in our study in concordance with the recommendation made by WHO expert consultation on diabetes for women.[24] Seventy-four percent of PCOS subjects and 32% of non-PCOS

Table 2: Various anthropometric parameters and hormonal levels in subjects

	PCOS group	Control group	*P*
Age (years)	26.5±3.23 (18–35)	26.02±4.16 (19–35)	0.574
Weight (kg)	63.26±12.77 (42–100)	61.14±9.84 (44–89)	0.355
Height (m)	1.56±0.06 (1.4–1.73)	1.54±0.04 (1.43–1.67)	0.101
BMI (kg/m²)	25.82±4.74 (18.42–41.62)	25.61±3.97 (18.55–38.08)	0.802
WC (cm)	88.56±9.83 (73–115)	82.28±9.69 (63–110)	0.002*
HC (cm)	100.78±8.50 (84–122)	96.94±8.63 (79–122)	0.027*
WHR	0.87±0.05 (100–132)	0.84±0.03 (0.76–0.94)	0.001*
Age at menarche (years)	13.04±1.19 (11–16)	12.2±1.6 (10–14)	0.0005*
TSH (mIU/L)	4.04±2.73 (1.2–17.8)	3.07±1.25 (1.11–7.43)	0.024*
LH (IU/L)	11.75±6.37 (2.5–28.12)	9.14±6.34 (2.72–40.52)	0.043*
FSH (IU/L)	7.15±2.75 (3.23–14.89)	7.08±3.84 (1.18–22.63)	0.926
Prolactin (ng/mL)	15.91±4.71 (4.31–28.1)	16.83±4.20 (8.96–24.76)	0.306
Oestradiol (pg/mL)	45.17±14.53 (21.45–84.76)	35.05±9.19 (13.46–65.32)	<0.001*
Progesterone (ng/mL)	0.27±0.12 (0.005–0.564)	0.39±0.22 (0.05–1.107)	0.001*
Testosterone (ng/dL)	44.61±15.96 (15–79.57)	24.85±9.91 (5.71–49.2)	<0.001*
FBS (mg/dL)	94.72±10.16 (76–119)	88.70±8.94 (74–124)	0.002*
Postprandial (mg/dL)	131.40±16.68 (102–172)	126.34±13.61 (102–162)	0.1

**P*-value at the significant level that is <0.05. Values are expressed as mean±SD, median (range). Student's *t*-test for continuous variables. PCOS=Polycystic ovary syndrome, BMI=Body mass index, TSH=Thyroid-stimulating hormone, FSH=Follicle-stimulating hormone, LH=Luteinising hormone, SD=Standard deviation, WC=Waist circumference, HC=Hip circumference, FBS=Fasting blood sugar, WHR=Waist/hip ratio

Table 3: Serum zinc levels and fasting insulin levels in the study groups

	PCOS group	Control group	*P*
Mean fasting insulin (µU/dL)	17.88±7.79 (2.64–39.53)	12.80±7.72 (2.66–40.14)	0.001*
Zinc (µg/dL)	122.00±26.72 (56.63–175.87)	134.89±23.06 (56.63–175.87)	0.012*

**P*-value at the significant level that is <0.05. Values are expressed as mean±SD, median (range). Student's *t*-test for continuous variables. SD=Standard deviation, PCOS=Polycystic ovary syndrome

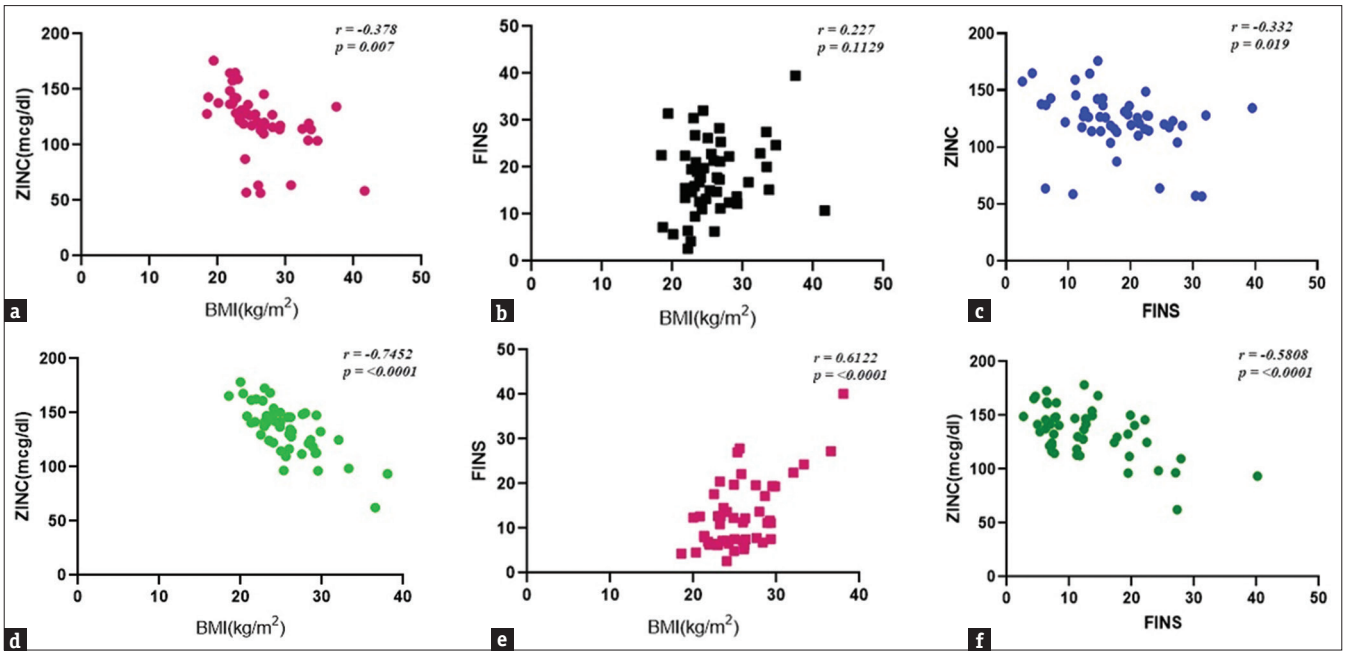

Figure 2: Pearson's correlation between serum zinc, fasting insulin levels and body mass index in the study groups. (a-c) Showing polycystic ovary syndrome group while (d-f) showing control group. BMI = Body mass index

subjects had WHR >0.85. The difference in mean values of WC and WHR was significant in both groups. Women with PCOS had a higher WC and WHR compared to non-PCOS subjects in spite of being BMI matched in our study. Similar results were observed in previous studies by Macut *et al*.[19] and Wiltgen *et al*.[20] where significantly higher WC in PCOS was observed. In the Indian study by Ganie *et al*.,[17] the mean WC was 81.30 ± 9.78 in subjects with PCOS and 81.29 ± 10.06 cm in subjects without PCOS.

Thus, even with comparable BMI, PCOS subjects were found to have higher values of WC and WHR than non-PCOS subjects. This reflects the tendency of central obesity amongst women with PCOS.

Zinc is a vital trace element essential for the regulation, structure and catalytic function of over 300 proteins, transcription factors and enzymes. In females, zinc deficiency can lead to complications such as abnormal ovarian development and impaired synthesis/secretion of FSH and LH.[25]

Even before any evidence emerged of a link between zinc and insulin within the β-cell, it was understood that adding zinc to insulin would prolong the effectiveness of a specific insulin dose. When insulin was initially prescribed for treating type 1 diabetes, zinc was added *in vitro* to extend insulin's action by delaying its absorption from the injection site.[26]

However, several articles have mentioned that serum zinc levels may not be the true indicator of intracellular zinc levels and, thus, zinc deficiency.[27,28] The inability of the techniques to measure the intracellular zinc levels in our study area set up was a drawback as we could only measure serum zinc levels in the subjects.

One possible mechanism for linking Zinc to PCOS can be through its effect on the insulin signalling system. Studies have indicated that in PCOS, insulin resistance stems from defects in insulin action beyond the receptor level,[15] with decreased zinc levels being associated with this insulin resistance.[29] In our study, we found serum zinc levels to be significantly lower in the PCOS group (122.00 ± 26.72 µg/dL) as compared to the non-PCOS group (134.89 ± 23.06 µg/dL) with a $P = 0.012$.

Previous studies have documented lower levels of zinc in the PCOS group in comparison to a non-PCOS control group. Studies include Kanafchian *et al*.[15] who documented lower zinc and selenium levels in PCOS subjects when compared to the control group. Another study conducted by Zheng *et al*.[30] also showed lower values of serum zinc in the PCOS group with a $P = 0.009$ and sample size of $n = 96$ (PCOS) and $n = 105$ (non-PCOS). Another study done by Guler *et al*.[31] showed lower statistically significant levels of serum zinc in PCOS and control group with a $P < 0.001$. Farhood *et al*.[25] and Kulhan *et al*.[32] did not find a significant relation between serum zinc levels and PCOS. Only one study conducted by Kurdoglu *et al*.[33] showed higher zinc levels in the PCOS group, but this study had selected patients with BMI in the normal range and

thus can be biased in the results. A meta-analysis of 123 articles conducted by Akhtar[34] has proposed a cut-off for serum zinc in the South Asian population, defining zinc deficiency to be 66 µg/dL for non-pregnant females. In our study, we found five patients in the PCOS group (10%) had serum zinc values <66 µg/dL, which is considered deficient. However, all the non-PCOS subjects had higher serum zinc levels than 66 µg/dL.

In our study, we found a negative correlation between zinc and fasting insulin ($r = -0.580$, $P < 0.0001$) in the control group and ($r = -0.332$, $P = 0.019$) in the case group. A previous meta-analysis done by Pearsey *et al*.[11] in which he took 14 studies and a total of 3127 participants has shown that zinc-alpha2-glycoprotein is responsible for dysglycemia and insulin resistance. Revathi *et al*.[35] also reported a statistically significant correlation between zinc and insulin resistance. In another study, zinc levels were found to be lower in the group with insulin resistance than in the PCOS patients without insulin resistance.[36]

Zinc supplements have also shown improved glycaemic as well as lipid profiles in PCOS patients.[13] Changes in serum trace element concentrations, as well as copper/zinc ratio, have been observed in women suffering from PCOS.[37,38] Studies have shown that one of the key players involved in the pathophysiology of PCOS is the higher generation of reactive oxygen species,[39] as it results in damage of the cell membrane lipids and lipid peroxidation.[36]

In PCOS, the redox imbalance is evident through an impaired antioxidative mechanism, characterized by reduced activity of catalase and glutathione peroxidase alongside elevated levels of malondialdehyde (MDA) concentration, which is a known oxidative stress biomarker.[36] In women with PCOS, following zinc supplementation, decreased lipid peroxidation (indicated by lower MDA concentrations) was also observed.[13,40]

Leptin resistance seen in obesity could have resulted from zinc deficiency, where zinc may either directly impact leptin gene expression or indirectly influence leptin production by enhancing glucose utilisation in adipose tissue.[41]

Older studies by Torkanlou *et al*.[42] and Di Martino *et al*.[43] have shown that obesity is associated with lower serum zinc levels. In our study, we found a negative statistically significant correlation between BMI and zinc in the PCOS subjects ($r = -0.378$, $P = 0.007$) and the non-PCOS subjects ($r = -0.7452$, $P < 0.0001$). In a previous study by Rios-Lugo *et al*.[44] a negative correlation between BMI and serum Zinc levels ($r = -0.663$ and $P < 0.001$) in both male and female subjects was observed. Another Korean study on metabolic syndrome patients has shown decreased zinc levels with increasing BMI of the population.[45]

We also documented a positive correlation between BMI and fasting insulin levels in both the PCOS subjects ($r = 0.227$, $P = 0.112$) and non-PCOS subjects ($r = 0.612$, $P < 0.0001$).

Most individuals with PCOS are either obese or overweight,[46] and research has demonstrated an inverse relationship between serum zinc levels and BMI in healthy individuals[47] as well as in PCOS patients.[25] In our study, the mean FBS levels were significantly higher (94.27 ± 10.16 mg/dL) in PCOS subjects and (88.70 ± 8.94 mg/dL) in non-PCOS subjects as with a $P = 0.002$. Five patients had FBS levels ≥110 mg/dL compared to only 1 of the non-PCOS subjects. None of the women had a blood glucose value of >126 mg/dL in the FBS parameter. The mean post-prandial glucose levels were (131.40 ± 16.68 mg/dL) in PCOS subjects and (126.34 ± 13.61 mg/dL) in non-PCOS subjects but were statistically not significant. The mean fasting insulin levels were (17.88 ± 7.79 mIU/L) in PCOS subjects and (12.80 ± 7.72 mIU/L) in normals with a $P = 0.001$. Nine women in the PCOS group had a serum fasting insulin level of >25, while only four had fasting serum insulin >25 in the non-PCOS group. Thus, similar to previous studies like Ganie *et al*.,[17] Mario *et al*.[21] and Macut *et al*.[19] in our study also, all FBS and fasting insulin levels were higher amongst PCOS subjects, which indicates a higher risk of diabetes mellitus and other endocrinological and cardiovascular disorders in Indian women with PCOS.

In our study, zinc and BMI were negatively correlated in both the PCOS and the non-PCOS groups. BMI and fasting insulin were positively correlated in the non-PCOS group. While, zinc and fasting insulin were negatively correlated in PCOS and non-PCOS groups.

Thus, it can be asserted that lower zinc levels were seen in patients with higher BMI in both groups. As in our study, fasting insulin is being used as a marker of insulin resistance this suggests a positive correlation between obesity and insulin resistance and assessing that lower zinc levels were linked to higher insulin resistance in both the groups. This shows that even in healthy controls, lower zinc levels were linked with insulin resistance, emphasising the importance of zinc in regulating insulin homeostasis.

It is also important to think that do the zinc levels indicate a dilutional effect due to high BMI or due to high utilisation of zinc in excess insulin secretion or not. This delineation can help steer further research

towards weight reduction and zinc supplementation to correct insulin resistance and hyperinsulinaemia. Thus, a follow-up study with zinc as a supplement in PCOS women diet and weight reduction in different groups can be done to get an accurate idea of the same. However, this is one of the few studies in the Indian population to study the values of serum zinc levels in PCOS women, and further studies need to be conducted with a larger sample size for establishing zinc levels and the role of supplementation in PCOS women.

Conclusion

This study concludes that zinc levels are significantly lower in PCOS subjects when compared to BMI-matched non-PCOS subjects, which might have metabolic implications in PCOS, thus perpetuating a vicious cycle of hormonal dysregulation and obesity. Therefore, optimising zinc-insulin homeostasis might be a helpful adjunct to lifestyle changes in tackling the ever-rising pandemic of PCOS and metabolic syndrome.

Author's contributions

SD - Concept, design, literature search, data acquisition and analysis, manuscript preparation, editing and review; RY - Concept, design, manuscript editing and review; AT - Data analysis, manuscript preparation, editing and review.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability statement

The data set used in the study is available with corresponding author.

References

1. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19-25.
2. Azziz R. Controversy in clinical endocrinology: Diagnosis of polycystic ovarian syndrome: The Rotterdam criteria are premature. J Clin Endocrinol Metab 2006;91:781-5.
3. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89:2745-9.
4. Wijeyaratne CN, Balen AH, Barth JH, Belchetz PE. Clinical manifestations and insulin resistance (IR) in polycystic ovary syndrome (PCOS) among South Asians and caucasians: Is there a difference? Clin Endocrinol (Oxf) 2002;57:343-50.
5. Abedini M, Ghaedi E, Hadi A, Mohammadi H, Amani R. Zinc status and polycystic ovarian syndrome: A systematic review and meta-analysis. J Trace Elem Med Biol 2019;52:216-21.
6. Gammoh NZ, Rink L. Zinc in infection and inflammation. Nutrients 2017;9:624.
7. Saper RB, Rash R. Zinc: An essential micronutrient. Am Fam Physician 2009;79:768-72.
8. Ilouz R, Kaidanovich O, Gurwitz D, Eldar-Finkelman H. Inhibition of glycogen synthase kinase-3beta by bivalent zinc ions: Insight into the insulin-mimetic action of zinc. Biochem Biophys Res Commun 2002;295:102-6.
9. Norouzi S, Adulcikas J, Sohal SS, Myers S. Zinc stimulates glucose oxidation and glycemic control by modulating the insulin signaling pathway in human and mouse skeletal muscle cell lines. PLoS One 2018;13:e0191727.
10. Baker EN, Blundell TL, Cutfield JF, Cutfield SM, Dodson EJ, Dodson GG, *et al.* The structure of 2Zn pig insulin crystals at 1.5 a resolution. Philos Trans R Soc Lond B Biol Sci 1988;319:369-456.
11. Pearsey HM, Henson J, Sargeant JA, Davies MJ, Khunti K, Suzuki T, *et al.* Zinc-alpha2-glycoprotein, dysglycaemia and insulin resistance: A systematic review and meta-analysis. Rev Endocr Metab Disord 2020;21:569-75.
12. Chimienti F, Favier A, Seve M. ZnT-8, a pancreatic beta-cell-specific zinc transporter. Biometals 2005;18:313-7.
13. Foroozanfard F, Jamilian M, Jafari Z, Khassaf A, Hosseini A, Khorammian H, *et al.* Effects of zinc supplementation on markers of insulin resistance and lipid profiles in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Exp Clin Endocrinol Diabetes 2015;123:215-20.
14. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41-7.
15. Kanafchian M, Mahjoub S, Esmaeilzadeh S, Rahsepar M, Mosapour A. Status of serum selenium and zinc in patients with the polycystic ovary syndrome with and without insulin resistance. Middle East Fertil Soc J 2018;23:241-5.
16. Misra A. Ethnic-specific criteria for classification of body mass index: A perspective for Asian Indians and American diabetes association position statement. Diabetes Technol Ther 2015;17:667-71.
17. Ganie MA, Marwaha RK, Dhingra A, Nisar S, Mani K, Masoodi S, *et al.* Observation of phenotypic variation among Indian women with polycystic ovary syndrome (PCOS) from Delhi and Srinagar. Gynecol Endocrinol 2016;32:566-70.
18. Jena D, Choudhury AK, Mangaraj S, Singh M, Mohanty BK, Baliarsinha AK. Study of visceral and subcutaneous abdominal fat thickness and its correlation with cardiometabolic risk factors and hormonal parameters in polycystic ovary syndrome. Indian J Endocrinol Metab 2018;22:321-7.
19. Macut D, Božić Antić I, Bjekić-Macut J, Panidis D, Tziomalos K, Vojnović Milutinović D, *et al.* Lipid accumulation product is associated with metabolic syndrome in women with polycystic ovary syndrome. Hormones (Athens) 2016;15:35-44.
20. Wiltgen D, Benedetto IG, Mastella LS, Spritzer PM. Lipid accumulation product index: A reliable marker of cardiovascular risk in polycystic ovary syndrome. Hum Reprod 2009;24:1726-31.
21. Mario FM, Graff SK, Spritzer PM. Adiposity indexes as phenotype-specific markers of preclinical metabolic alterations and cardiovascular risk in polycystic ovary syndrome: A cross-sectional study. Exp Clin Endocrinol Diabetes 2017;125:307-15.
22. Wanderley MD, Pereira LC, Santos CB, Cunha VS, Neves MV. Association between insulin resistance and cardiovascular risk factors in polycystic ovary syndrome patients. Rev Bras Ginecol

Obstet 2018;40:188-95.
23. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. Circulation 2002;106:3143-421.
24. World Health Organization. Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:i-253.
25. Farhood IG. Assessment of serum zinc level in patients with polycystic ovary syndrome. Iraqi J Med Sci 2017;15:39-47. Available from: https://www.iasj.net/iasj/article/126396. [Last accessed on 2021 Apr 18].
26. Quianzon CC, Cheikh I. History of insulin. J Community Hosp Intern Med Perspect 2012;2:18701. [doi: 10.3402/jchimp.v2i2.18701].
27. Hennigar SR, Lieberman HR, Fulgoni VL 3rd, McClung JP. Serum zinc concentrations in the US population are related to sex, age, and time of blood draw but not dietary or supplemental zinc. J Nutr 2018;148:1341-51.
28. Hess SY, Peerson JM, King JC, Brown KH. Use of serum zinc concentration as an indicator of population zinc status. Food Nutr Bull 2007;28:S403-29.
29. Taylor CG. Zinc, the pancreas, and diabetes: Insights from rodent studies and future directions. Biometals 2005;18:305-12.
30. Zheng G, Wang L, Guo Z, Sun L, Wang L, Wang C, *et al.* Association of serum heavy metals and trace element concentrations with reproductive hormone levels and polycystic ovary syndrome in a Chinese population. Biol Trace Elem Res 2015;167:1-10.
31. Guler I, Himmetoglu O, Turp A, Erdem A, Erdem M, Onan MA, *et al.* Zinc and homocysteine levels in polycystic ovarian syndrome patients with insulin resistance. Biol Trace Elem Res 2014;158:297-304.
32. Kulhan M, Kulhan N, Nayki U, Nayki C, Ata N, Ulug P, *et al.* Assessment of the relationship between serum Vitamin (A, B 12, C, D, folate) and zinc levels and polycystic ovary syndrome. Arch Med Sci Civiliz Dis 2017;1:62-9.
33. Kurdoglu Z, Kurdoglu M, Demir H, Sahin HG. Serum trace elements and heavy metals in polycystic ovary syndrome. Hum Exp Toxicol 2012;31:452-6.
34. Akhtar S. Zinc status in South Asian populations – An update. J Health Popul Nutr 2013;31:139-49.
35. Revathi R, Julius A, Singaravelu S. Correlation of serum copper, zinc, magnesium with insulin resistance in Pcos female of reproductive age group. Int J Pharm Res 2018;10:789-92.
36. Özer A, Bakacak M, Kıran H, Ercan Ö, Köstü B, Kanat-Pektaş M, *et al.* Increased oxidative stress is associated with insulin resistance and infertility in polycystic ovary syndrome. Ginekol Pol 2016;87:733-8.
37. Sharif ME, Adam I, Ahmed MA, Rayis DA, Hamdan HZ. Serum level of zinc and copper in Sudanese women with polycystic ovarian syndrome. Biol Trace Elem Res 2017;180:23-7.
38. Li M, Tang Y, Lin C, Huang Q, Lei D, Hu Y. Serum macroelement and microelement concentrations in patients with polycystic ovary syndrome: A cross-sectional study. Biol Trace Elem Res 2017;176:73-80.
39. González F, Rote NS, Minium J, Kirwan JP. Reactive oxygen species-induced oxidative stress in the development of insulin resistance and hyperandrogenism in polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91:336-40.
40. Maktabi M, Jamilian M, Asemi Z. Magnesium-zinc-calcium-Vitamin D Co-supplementation improves hormonal profiles, biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Biol Trace Elem Res 2018;182:21-8.
41. Mantzoros CS, Prasad AS, Beck FW, Grabowski S, Kaplan J, Adair C, *et al.* Zinc may regulate serum leptin concentrations in humans. J Am Coll Nutr 1998;17:270-5.
42. Torkanlou K, Bibak B, Abbaspour A, Abdi H, Saleh Moghaddam M, Tayefi M, *et al.* Reduced serum levels of zinc and superoxide dismutase in obese individuals. Ann Nutr Metab 2016;69:232-6.
43. Di Martino G, Matera MG, De Martino B, Vacca C, Di Martino S, Rossi F. Relationship between zinc and obesity. J Med 1993;24:177-83.
44. Rios-Lugo MJ, Madrigal-Arellano C, Gaytán-Hernández D, Hernández-Mendoza H, Romero-Guzmán ET. Association of serum zinc levels in overweight and obesity. Biol Trace Elem Res 2020;198:51-7.
45. Seo JA, Song SW, Han K, Lee KJ, Kim HN. The associations between serum zinc levels and metabolic syndrome in the Korean population: Findings from the 2010 Korean national health and nutrition examination survey. PLoS One 2014;9:e105990.
46. McCartney CR, Marshall JC. Clinical practice. Polycystic ovary syndrome. N Engl J Med 2016;375:54-64.
47. Ghayour-Mobarhan M, Taylor A, New SA, Lamb DJ, Ferns GA. Determinants of serum copper, zinc and selenium in healthy subjects. Ann Clin Biochem 2005;42:364-75.