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Original Research Article

Prospective Observational Evaluation of the Serum Levels of Zinc, Copper and Magnesium in Polycystic Ovarian Syndrome

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Abstract

Aim: Evaluation of serum levels of zinc, copper and magnesium in polycystic ovarian syndrome.

Material and methods: This prospective observational study was carried out in the Department of Obstetrics and Gynecology, Netaji Subhas Medical College and Hospital, Bihta, Patna, Bihar, India for 11 months. A total of 200 patients were included in the study and they were further divided into two groups i.e.100 cases and 100 healthy control of age group (15-36 years) from same socioeconomic status.

Results: Serum zinc levels in PCOS women and control group were 167.31± 6.8 mcg/dl and 156.48 ±1.6 mcg/dl respectively and the difference was significant. It was found that except for the age category of 30- 35 years, all other age categories (15- 30 years) had significantly higher levels of serum zinc concentration among study group as compared to controls. Mean serum copper levels in study group was 201±37.66 mcg/dl and in control group was 231.59± 51.88 mcg/dl ($p< 0.01$). Serum copper levels were found to be significantly lower in the patients with younger age categories i.e. 15-20 years and 20-25 years (p= 0.87 and 0.356). Present study depicted significantly higher serum magnesium levels in study group (2.16 ± 0.13meq/l) as compared to the control group (1.94 ±0.08meq/l).

Conclusion: Serum zinc and magnesium levels were found significantly higher among study group (women with PCOS) than control group in the present study. Higher serum zinc concentrations have been related to increased oxidative stress in PCOS women. Serum copper levels were found to be significantly lower in study group as compared to control group, though they were above the normal range in both the groups.

Keywords: Zinc levels, Magnesium levels, PCOS

Introduction:

Polycystic ovary syndrome (PCOS) is a multifactorial and polygenic disorder of the endocrine system characterized by anovulation, hyperandrogenism, and polycystic ovarian morphology.[1] According to different diagnostic criteria, the global prevalence of PCOS ranges from 4 to 21%[2] Women with PCOS have significant reproductive effects, including increased risk of infertility, miscarriage, and pregnancy-related complications[3] , along with metabolic disorders, such as obesity[4] , insulin resistance (IR)[5] , and type 2 diabetes mellitus.[6] The causes of PCOS are currently unclear and no effective biomarkers for early PCOS screening have been identified to date.[7] Recently, alterations in trace element levels in PCOS have attracted considerable research attention.[8] Trace elements, such as zinc (Zn), copper (Cu) and magnesium (Mg), are essential for normal cellular functions, and play major roles in metabolic pathways involving of enzymes, hormones, and vitamins.[9] Considerable evidence suggests that abnormal levels of trace elements are associated with metabolic syndrome[10] and PCOS is characteristically accompanied by metabolic dysfunction. However, epidemiological findings on the associations between trace elements and PCOS are inconsistent. For example, Revathi et al.[11] showed that serum levels of Cu and Zn were higher while Mg levels were lower in PCOS patients than the control group. In contrast, Li et al.[12] reported no significant differences in the levels of serum Zn, Mg, and iron (Fe) between PCOS and healthy control groups in a Chinese cohort. A meta-analysis conducted by Spritzer and co-workers in 2015 did not offer a robust conclusion, since only four related articles were included that used the same unit of measurement for specific trace elements.[8] In view of the increased related epidemiological evidence in recent years.[13,14] , meta analysis data need to be urgently updated. Standardized mean difference (SMD) is a practical meta-analysis statistical method to overcome the inconsistencies in measurement units among different studies.[15]

Material and methods

This prospective observational study was carried out in the Department of Obstetrics and Gynecology, Netaji Subhas Medical College and Hospital, Bihta, Patna, Bihar, India for 11 months. A total of 200 patients were included in the study and they were further divided into two group's i.e.100 cases and 100 healthy control of age group (15-36 years) from same socioeconomic status.

Methodology

Patients taking multivitamin/mineral supplements for last 2 months Hormonal drugs / OCPs in past 6 weeks, patients having any Thyroid/Renal/Liver disorder and Diabetes mellitus were excluded from the study. Pregnant and lactating women were also be excluded from the study. Detailed history such as age menstrual history, past medication, Obs history, personal and family history was taken. Height and weight of all subjects were obtained and BMI was calculated by dividing weight by height square (kg/m^2). Standard laboratory investigations such as Hb, lipid profile, fasting blood sugar, and thyroid profile etc. were done in all the patients. For clinical evaluation, hirsutism score was calculated (<4- mild, 4-7- moderate, ≥8 – severe). Hirsutism was scored according to modified Ferriman

Gallaway score. Samples for estimation of serum zinc copper, magnesium and vit D were drawn from antecubital vein in a sterile syringe. The blood was allowed to clot at

room temperature for 30 min and serum was separated by centrifugation at 3000 rpm for 10 minutes. The samples were stored at -20 degree Celsius till further analysis.

Serum zinc and copper levels were analysed by using colorimetric method. Serum magnesium levels were done by using xylidyblue – 1 at alkaline pH yield a proper coloured at OD (660 nm). Serum level of minerals (zinc, copper and magnesium) and vitamin D in PCOS patients and healthy control of age group (15-35years) were compared in the present study.

Interpretation of serum levels

- Copper >155 µg/dL (normal range 80-155 µg/dL)* was considered as high levels of serum copper and <80 was considered as deficient Zinc (normal range 60-120 µg/dL)* – patients having zinc level <60 µg/dl was considered as deficient.
- Magnesium (normal range 1.3-2.5 meq/L)* – patients having Mg level <1 meq/L was considered as deficient.
- Vit. D (normal range 30-100 ng/mL)* – patients having vit. D level < 20ng/ml was considered as deficient.

Statistical analysis

The quantitative parameters were expressed as mean with standard deviation (Mean±SD) in both the groups. p value was calculated by using student t-test and chi-square (□2) test.

Statistical significance was considered as $p<0.05$. Statistical Package for Social Sciences [SPSS] version 25.0 was used for analysis.

Results

Table 1: Body mass index

BMI	Study Group (n=100)	Control Group (n=100)
<18.5 kg/m^2 (underweight)	1 (1%)	0
18.5-24.99 kg/m^2 (normal)	49 (49%)	77 (77%)
25-29.99 kg/m^2 (overweight)	29 (29%)	23 (23%)
>30 kg/m^2 (obese)	21 (21%)	0

Independent t-test, p-value<0.01

Table 2: Comparison of clinical, laboratory parameters and micronutrients between 2 groups

Variable	Study group (n=100) Mean ± SD	Control group (n=100) Mean ± SD	p-value
Age	24.43±4.53	24.81 ± 3.65	0.471
BMI (kg/m^2) (Mean ± SD)	26.17±3.99	23.53±2.44	<0.01
Haemoglobin (g/dl)	10.89±1.38	12.81±1.09	<0.01
TSH (mIU/L)	3.56±2.70	3.71±1.03	0.561
RBS (mg/dl)	112.16±10.23	108.78 ± 6.55	<0.05
Cholesterol (mg/dl)	181.60± 45.41	175.27± 23.00	0.159
HDL (mg/dl)	41.84 ± 9.64	43.53 ± 8.62	0.220
LDL (mg/dl)	140.82 ±27.61	135.83 ± 14.33	0.058
TG(mg/dl)	128.63 ± 39.5	123.80 ± 22.98	0.239
Serum zinc (µg/dl)	167.31±6.83	156.48±11.68	<0.01

Serum Copper (µg/dl)	201.97±37.66	231.59±51.88	<0.01
Serum Magnesium(meq/L)	2.16±0.13	1.94±0.18	<0.01

Table 3: Degree of association between micronutrients and PCOS

Variable	Unadjusted odd's ratio	95% CI	P-value
S. zinc(µg/dl)	1.232	1.191-1.174	<0.001
S. copper(µg/dl)	0.996	0.990-0.992	<0.001

Most of the women belonged to 20-25 years age group in both the groups in the present study. The mean BMI in study group and control group was 26.17 ± 3.99 kg/m^2 and 23.53 ± 2.44 kg/m^2 respectively and the difference was significant (p< 0.01) (Table 1). In Table 2, haemoglobin levels were found to be significantly higher among controls as compared to PCOS. Blood sugar levels were higher among study group with mean value of 112.16 ± 10.3mg/dl as compared to controls where this value was 108.78 ± 16.55 mg/dl and the difference was statistically significant.

High levels of serum zinc, copper and magnesium in women of study group and the control group. Also, there was significant difference in the serum levels of zinc, copper and magnesium between the study group and control group**.** Serum zinc levels in PCOS women and control group were 167.31± 6.8 mcg/dl and

156.48 ±1.6 mcg/dl respectively and the difference was significant. It was found that except for the age category of 30- 35 years, all other age categories (15- 30 years) had significantly higher levels of serum zinc concentration among study group as compared to controls. Mean serum copper levels in study group was 201±37.66 mcg/dl and in control group was 231.59± 51.88 mcg/dl (p< 0.01). Serum copper levels were found to be significantly lower in the patients with younger age categories i.e. 15-20 years and 20-25 years (p= 0.87 and 0.356). Present study depicted significantly higher serum magnesium levels in study group (2.16 ± 0.13meq/l) as compared to the control group (1.94 ±0.08meq/l).

Discussion

Polycystic ovarian disease is a heterogeneous, multisystem endocrinopathy in a women of reproductive age group affecting 5-21 % of women.[16] It is a clinical diagnosis characterised by the presence of 2 or more of the following feature: chronic oligoovulation or anovulation, androgen excess and polycystic ovaries with the exclusion of other etiologies. It is associated with short term reproductive and long term metabolic dysfunctions. The mechanistic links between obesity, hyperinsulinemia and anovulation have been investigated to a larger extent, still the pathogenesis of PCOS remain unclear. There might be an involvement of trace elements in the pathophysiology of PCOS.

The mean BMI in study group was statistically higher in PCOS women as compared to control group (p< 0.01). Similar result were concluded in the studies by Rajeshwari *et al*, Zheng *et al.* and Li *et al*.[17-19] Hence, obesity plays a crucial role in the development and maintenance of PCOS and strongly influences the severity of its clinical and endocrine features.

Blood sugar levels were higher among study group with mean value of 112.16 ± 10.3mg/dl as compared to controls where this value is

108.78 ± 16.55 mg/dl. There was significant difference between the mean blood sugar values of study group and control group and it was comparable to the study of Kumar *et al*.[20] This contributes to the fact that pathogenesis of PCOS is linked to the development of IR (insulin resistance) and hyperinsulinemia which in turn progress to long term risks of DM (Diabetes Mellitus) type II with its associated microvascular and macrovascular complications. Therefore, women with PCOS should be screened for DM on regular basis.

In present study, total cholesterol, LDL and triglyceride levels were higher while HDL levels were found to be low in study group as compared to control group, but the difference was not statistically significant. The similar results in both group may be due to same environmental factors such as diet and physical exercise. Bahecci *et al*. concluded that after oral fat tolerance test, triglyceride, total cholesterol, and VLDL values were higher in patients with PCOS and results of present study were not comparable with this study.[21] In present study, there were high levels of serum zinc, copper and magnesium in women of study group and the control group. Also, there was significant difference in the serum levels of zinc, copper and magnesium between the study group and control group. High baseline serum concentration of these micro- nutrients may be attributed to the socio-cultural and environmental characteristics of this population. These high levels have been demonstrated by other studies also done in northern part of India. According to study of Taneja *et al*, serum zinc levels were significantly higher in population of Chandigarh as zinc levels were more in crops grown there.[22] It had also been studied that, Mg2+, Ca2+, NO3- and SO42- were significantly higher in rain water in northern India due to greater atmospheric pollution.[23] In the present study, serum zinc levels in PCOS women and control group were 167.31+- 6.8 mcg/dl and 156.48 +-1.6 mcg/dl respectively and the difference was significant and it was comparable to the other studies.[24] and not comparable with Mazloomi *et al* and Zheng *et al*.[17,25] Such differences may be attributed to many factors, such as hormone levels and Insulin Resistance (IR), which can affect serum zinc concentrations in PCOS patients. Another possible rationale for this finding could be inter-nation dietary habit variations as all of the reported studies were conducted among non-Africans.

In present study, the mean serum copper levels in study group was 201+-97.66 mcg/dl and in control group was 231.59+- 51.88 mcg/dl ($p< 0.01$). In present study, serum copper in PCOS women were significantly lower than the controls and it was not comparable to study of Zheng G *et al*, Li M *et al* and Celik *et al*.[17,20,26] It may be due to difference in methods of measuring serum copper levels or dietary variations. Serum copper levels were found to be significantly lower in the patients with younger age categories i.e. 15-20 years and 20-25 years (p= 0.87 and 0.356).

Present study depicted significantly higher serum magnesium levels in study group (2.16 ± 0.13meq/l) as compared to the control group (1.94 +-0.08meq/l). Changes in serum magnesium concentrations are controversial. Although, Kurdoglu *et al.* also observed higher mean of serum magnesium levels in study group but it was statistically non-significant.[24] However, Rajeswari *et al.* and Swetha *et al.* had reported a lower serum Mg level in study group, while Li *et al.* had noted no significant difference between study group and the control group.[12,27] Increased serum magnesium levels in present study may be due to environmental and dietary variations.

Li *et al* showed that women with hirsutism had significantly lower levels of serum magnesium as compared to women without hirsutism (p=0.037) and signifies that magnesium may be associated with hirsutism. The levels of serum copper (p=0.133) and zinc (p =0.100) were insignificant in PCOS women with and without hirsutism [25].

Conclusion

Serum zinc and magnesium levels were found significantly higher among study group (women with PCOS) than control group in the present study. Higher serum zinc concentrations have been related to increased oxidative stress in PCOS women. Serum copper levels were found to be significantly lower in study group as compared to control group, though they were above the normal range in both the groups.

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