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Serum levels of zinc, copper and magnesium in polycystic ovarian syndrome: A cross Sectional study

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Abstract
Introduction: Polycystic ovarian syndrome is the most common endocrinopathy affecting approximately 5 to 21% of reproductive age women. Although the exact aetiology of PCOS is unknown, recent reports have indicated the association between PCOS and disturbance in trace elements (e.g. zinc, copper and magnesium) levels and oxidative stress.
Aim and Objective: To compare serum levels of essential trace elements Zinc (Zn), Copper (Cu) and Magnesium (Mg) among patients with PCOS and healthy controls of age group (15-35 years) from same socio economic status.
Material and Methods: Present study was carried out in 240 patients (120 cases and 120 healthy controls) of age group (15-35 years) and serum levels of Zinc, Copper and magnesium were compared in PCOS women and healthy controls by using colorimetric method
Results: High baseline serum concentration of zinc, copper and magnesium were found in both i.e. women with PCOS and the healthy controls and it may be attributed to the socio-cultural and environmental characteristics of this population. Serum zinc and magnesium levels were found to be significantly higher while serum copper levels were significantly lower in women with PCOS in comparison to healthy controls in present study.
Conclusion: The results of the present study provide clues to explore the role of trace elements in pathogenesis of PCOS and provide an area of interest for further clinical trials in PCOS.

Keywords: zinc, copper, magnesium and polycystic ovarian syndrome

Introduction

Polycystic ovarian disease is a heterogenous, multisystem endocrinopathy in women of reproductive age group affecting 5 to 21 percent of women of this age group (15-45 years) [1]. This disease discovered by and named as Stein Leventhal syndrome [2]. The underlying pathogenesis of PCOS are insulin resistance and compensatory hyper-insulinemia [3]. The most common characteristic of PCOS is irregular menstrual period.

The Rotterdam criteria defines PCOS by the presence of two of the three following features: 1) Oligo –ovulation or anovulation, 2) clinical or biochemical signs of hyperandrogenism., 3) polycystic ovaries on ultrasound 12 or more follicles measuring 2-9mm in each ovary with an ovarian volume of >10 ml [4].

PCOS diagnosis according to NIH consensus, necessitates the existence of oligo or amenorrhoea and hyperandrogenaemia without a known disorder that explain the cause of hyperandrogenaemia [5]. Although the exact aetiology of PCOS is unknown, recent reports have indicated the association between PCOS and disturbance in trace elements (e.g. zinc, copper and magnesium) levels and oxidative stress [1-3]. The importance of essential trace metals in health and disease is indisputable because of their vital role in specific concentration ranges and toxicity at relatively high levels. Essential trace elements have four major functions as being stabilizers, elements of structure, essential elements for hormonal function and cofactors in enzymes [6].

Zinc (Zn) is essential for the structure of many enzymes and plays a fundamental role in approximately 300 enzymatic reactions. Zinc is a potent antioxidant and its deficiency causes oxidative damage in multiple organ including the heart. So, zinc deficiency is a contributing risk factor for developing of metabolic and cardiovascular disease related to PCOS [7].

Role of copper in regulation of hypothalamic pituitary axis functioning was proven in number of works Change in serum copper level is associated with oxidative stress activation, in which

copper acts as a catalyst [8]. Both low and high copper concentrations are linked to the development of oxidative stress as decreased serum copper levels lowers antioxidant enzyme activity and increased serum copper levels causes development of Fenton reaction [9-10]. Copper level is correlated with change in carotid intima thickness and brachial flow mediated dilatation in PCOS patients. Thus increased copper level is responsible for increased risk of early vascular disease in women with PCOS.[11]

Magnesium is an important cofactor for enzymes involved in carbohydrate metabolism [12-3]. Magnesium is necessary for insulin secretion and magnesium replacement in those with Mg deficiency restores insulin secretion [14]. Decrease in intracellular magnesium concentration is associated with impaired glucose tolerance and increased risk for type 2 diabetes [15].

Magnesium plays an important role in supporting cardiovascular health. Low magnesium in PCOS patients are at increased risk of heart disease [16].

With this background, we thought that there might be a role of trace elements in the pathogenesis of PCOS. So present study was designed to compare the serum levels of zinc copper and magnesium in women with PCOS in comparison to healthy controls.

Material and Methods

A total of 240 patients were included in the study and they were further divided into two groups i.e.120 cases and 120 healthy control of age group (15-35 years) from same socioeconomic status. This study was conducted in the Department of Obstetrics and Gynaecology, Pt. B.D. Sharma PGIMS, Rohtak on patients attending the gynaecology OPD (out patient department) with diagnosis of PCOS. The diagnosis of PCOS was made on the basis of Rotterdam criteria.

Exclusion criteria: 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 temperatue 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.

* As per PGIMS Biochemistry laboratory

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 (χ^2) test.

Statistical significance was considered as $p<0.05$.

Statistical Package for Social Sciences [SPSS] version 20 was used for analysis.

Observations & Results

Table 1: Body mass index

BMI	Study Group (n=120)	Control Group (n=120)
<18.5 kg/m^2 (underweight)	1 (0.8%)	0
18.5-24.99 kg/m^2 (normal)	60 (50%)	93 (77.5%)
25-29.99 kg/m^2 (overweight)	34 (28.3%)	27 (22.5%)
≥30 kg/m^2 (obese)	25 (20.8%)	0

Independent t-test, p-value<0.01

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

Variable	Study group (n=120) Mean ± SD	Control group (n=120) Mean ± SD	p-value
Age	24.33±4.53	24.71 ± 3.65	0.481
BMI (kg/m^2) (Mean ± SD)	26.07±3.99	23.43±2.44	<0.01
Haemoglobin (g/dl)	10.99±1.38	12.71±1.09	<0.01
TSH (mIU/L)	3.46±2.70	3.61±1.03	0.571
RBS (mg/dl)	112.06±10.23	108.68 ± 6.55	<0.05
Cholesterol (mg/dl)	181.59± 45.41	175.17± 23.00	0.169
HDL (mg/dl)	41.94 ± 9.64	43.43 ± 8.62	0.210
LDL (mg/dl)	140.92 ± 27.61	135.73 ± 14.33	0.068
TG(mg/dl)	128.53 ± 39.5	123.70 ± 22.98	0.249
Serum zinc (µg/dl)	167.21±6.83	156.38±11.68	<0.01
Serum Copper (µg/dl)	201.87±37.66	231.49±51.88	<0.01
Serum Magnesium(meq/L)	2.06±0.13	1.84±0.08	<0.01

Table 3: Degree of association between micronutrients and PCOS

Variable	Unadjusted odd's ratio	95% CI	P-value
S. zinc(µg/dl)	1.132	1.091-1.174	<0.001
S. copper(µg/dl)	0.986	0.980-0.992	<0.001

Most of the women belonged to 21-25 years age group in both the groups in the present study. The mean BMI in study group and control group was 26.07 ± 3.99 kg/m^2 and 23.43 ± 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 112.06 ± 10.3mg/dl as compared to controls where this

value was 108.68 ± 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 167.21+- 6.8 mcg/dl and 156.38 +-1.6 mcg/dl respectively and the difference was significant. It was found that except for the age category of 31-35 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 231.49+-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 21-25 years (p= 0.97 and 0.366). Present study depicted significantly higher serum magnesium levels in study group (2.06 +- 0.13meq/l) as compared to the control group (1.84 +-0.08meq/l).

Discussion

Polycystic ovarian disease is a heterogenous, multisystem endocrinopathy in a women of reproductive age group affecting 5-21 % of women[1]. It is a clinical diagnosis characterised by the presence of 2 or more of the following feature: chronic oligo-ovulation 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*. [5, 19, 20] 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 112.06 ± 10.3mg/dl as compared to controls where this value is 108.68 ± 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*. [17] 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 167.21+- 6.8 mcg/dl and 156.38 +-1.6 mcg/dl respectively and the difference was significant and it was comparable to the other studies [18, 20, 24] and not comparable with Mazloomi *et al* and Zheng *et al*. [5, 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+-37.66 mcg/dl and in control group was 231.49+-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*. [5, 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 21-25 years (p= 0.97 and 0.366).

Present study depicted significantly higher serum magnesium levels in study group (2.06 +- 0.13meq/l) as compared to the control group (1.84 +-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 [11, 20, 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. This could be due to difference in ethnicity, religion, dietary habits and environmental factors and further studies are required to elucidate the role of copper in pathogenesis of PCOS. These results provide clues to explore the role of trace elements in pathogenesis of PCOS and provide an area of interest for further clinical trials in PCOS.

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