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CIRCULATING CORTISOL AND MAGNESIUM IN POLYCYSTIC OVARY SYNDROME: EXPLORING THEIR ASSOCIATION IN A CASE–CONTROL STUDY

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ABSTRACT

Introduction: Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting women of reproductive age and is associated with metabolic disturbances such as insulin resistance and obesity [1,2]. Cortisol, a stress hormone, and magnesium, an essential micronutrient involved in glucose metabolism, may play important roles in the pathophysiology of PCOS [3,4].

Aim: To evaluate and compare serum cortisol and magnesium levels in women with PCOS and healthy controls.

Materials and Methods: This case–control study was conducted in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynecology at a tertiary care hospital. A total of 220 women aged 18–35 years were included, comprising 110 PCOS patients and 110 healthy controls. PCOS was diagnosed according to Rotterdam criteria [1]. Serum cortisol levels were estimated using chemiluminescent immunoassay, while serum magnesium levels were measured by colorimetric method. Statistical analysis was performed using SPSS version 25. Independent t-test and Pearson correlation were applied.

Results: The mean serum cortisol level in PCOS patients was 19.2±4.5 µg/dL, significantly higher than in controls (13.1±3.2 µg/dL, $p<0.001$). Mean serum magnesium levels were significantly lower in PCOS patients (1.58±0.24 mg/dL) compared to controls (2.03±0.19 mg/dL, $p<0.001$). A significant negative correlation was observed between cortisol and magnesium levels in PCOS subjects ($r = -0.46$, $p<0.001$).

Conclusion: Women with PCOS showed significantly higher cortisol levels and lower magnesium levels compared to healthy controls. These findings suggest that stress-related hormonal imbalance and micronutrient deficiency may contribute to the metabolic abnormalities associated with PCOS.

KEYWORDS: Polycystic ovary syndrome, cortisol, magnesium, insulin resistance, stress hormones

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age, with a prevalence ranging from 6–10% worldwide [1,2]. It is characterized by hyperandrogenism, chronic anovulation, and polycystic ovarian morphology, according to the Rotterdam diagnostic criteria [1].

In addition to reproductive abnormalities, PCOS is strongly associated with metabolic disturbances such as insulin resistance, obesity, dyslipidemia, and an increased risk of type 2 diabetes mellitus [5,6]. These metabolic abnormalities contribute significantly to long-term complications including cardiovascular disease and metabolic syndrome [7].

Cortisol is the principal glucocorticoid hormone produced by the adrenal cortex and plays an essential role in glucose metabolism, stress response, and immune regulation [3]. Activation of the hypothalamic–pituitary–adrenal (HPA) axis leads to increased cortisol secretion, which may contribute to visceral adiposity and insulin resistance [8]. Several studies have suggested that women with PCOS exhibit altered HPA axis activity and increased cortisol levels compared to healthy individuals [9].

Magnesium is an important intracellular cation involved in more than 300 enzymatic reactions, including those regulating glucose metabolism and insulin signaling [4]. Magnesium deficiency has been linked to insulin resistance, chronic inflammation, and metabolic syndrome [10]. Previous studies have demonstrated that women with PCOS often exhibit reduced serum magnesium levels, which may exacerbate metabolic abnormalities associated with the disorder [11].

The interaction between cortisol and magnesium may play a crucial role in metabolic regulation. Chronic stress and elevated cortisol levels can lead to increased urinary excretion of magnesium, potentially resulting in magnesium deficiency [12].

Understanding the relationship between cortisol and magnesium levels in PCOS may provide valuable insights into the metabolic disturbances associated with this condition.
Hence, the present study was undertaken to evaluate serum cortisol and magnesium levels in women diagnosed with PCOS and compare them with healthy controls.

Aim

To evaluate and compare serum cortisol and magnesium levels in women with PCOS and healthy controls.

MATERIALS AND METHODS

Study Design and Ethical Considerations

This observational case–control study was conducted over a six-month period in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynecology at a tertiary care teaching hospital. The study protocol was reviewed and approved by the Institutional Ethics Committee, adhering strictly to the ethical standards outlined in the Declaration of Helsinki. Prior to enrolment, all eligible participants received detailed information regarding the study objectives, and written informed consent was documented.

Study Population and Participant Selection

A total of 220 female participants aged 18–35 years were enrolled and allocated equally into two distinct cohorts:

- PCOS Group (n=110): Women clinically diagnosed with Polycystic Ovary Syndrome (PCOS) following the revised 2003 Rotterdam consensus criteria, requiring the presence of at least two of the following:
  - Oligo- or anovulation
  - Clinical and/or biochemical signs of hyperandrogenism
  - Polycystic ovarian morphology on pelvic ultrasonography
- Control Group (n=110): Age-matched, healthy eumenorrheic females with regular menstrual cycles (21–35 days) and no clinical evidence of hyperandrogenism or endocrine abnormalities.

Exclusion Criteria

To minimize confounding factors affecting endocrine and electrolyte dynamics, individuals presenting with any of the following conditions were excluded from both groups:

- Established diabetes mellitus or impaired fasting glucose
- Thyroid dysfunction (hypothyroidism or hyperthyroidism)
- Hyperprolactinemia or Cushing's syndrome
- Chronic hepatic, renal, or cardiovascular diseases

Current or recent intake (within the preceding three months) of hormonal contraceptives, glucocorticoids, insulin sensitizers, anti-androgens, or magnesium supplements.

Blood Sampling and Specimen Processing

Following an overnight fast of 10–12 hours, 5 mL of venous blood was collected from the antecubital vein of each participant between 08:00 AM and 09:00 AM to account for the diurnal variation of hormonal secretion. In regularly menstruating controls, sampling was timed during the early follicular phase (days 2–5 of the menstrual cycle).
Samples were drawn under strict aseptic precautions using plain evacuated tubes (without anticoagulant). The blood was allowed to clot at room temperature for 30 minutes and subsequently centrifuged at 3000 rpm for 10 minutes at 4°C. The separated serum was aliquoted into sterile cryovials and stored at −20°C until biochemical quantification, avoiding repeated freeze-thaw cycles.

Biochemical Investigations

Serum parameters were measured according to standard laboratory quality control protocols:

- Serum Cortisol: Quantified via a two-site sandwich chemiluminescent immunoassay (CLIA) utilizing an automated clinical chemistry analyzer.
- Serum Magnesium: Estimated colorimetrically using the Xylidyl blue reaction method, where magnesium reacts with xylidyl blue in an alkaline medium to form a colored complex measured spectrophotometrically at 520 nm.

Both intra-assay and inter-assay coefficients of variation (CV) were verified to remain within acceptable limits (CV<5%).

Statistical Analysis

Statistical processing was carried out using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed data were expressed as mean ± standard deviation (SD).
Inter-group differences between PCOS cases and controls were evaluated using the independent samples t-test. Bivariate associations between serum cortisol, serum magnesium, and clinical parameters were determined using Pearson's correlation coefficient (r). A two-tailed p-value of <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 220 participants were included in the study, consisting of 110 women diagnosed with PCOS and 110 healthy controls.

The mean age of women in the PCOS group was 25.1 ± 4.1 years, while the mean age of the control group was 24.6 ± 3.8 years. The difference in age between the two groups was not statistically significant (p = 0.36), indicating that both groups were comparable in terms of age.

However, significant differences were observed in anthropometric parameters. The mean Body Mass Index (BMI) of women with PCOS was 27.8 ± 3.6 kg/m², which was significantly higher than that of the control group (23.7 ± 2.9 kg/m²) with a p-value <0.001. Similarly, the mean waist circumference was significantly higher in the PCOS group (91.4 ± 7.8 cm) compared to controls (80.2 ± 6.4 cm), and this difference was also statistically significant (p <0.001).

Serum cortisol levels were markedly elevated in women with PCOS. The mean serum cortisol level in the PCOS group was 19.2 ± 4.5 µg/dL, whereas in the control group it was 13.1 ± 3.2 µg/dL. The difference between the two groups was highly statistically significant (p <0.001), indicating increased cortisol levels in women with PCOS.

In contrast, serum magnesium levels were significantly reduced in women with PCOS compared to healthy controls. The mean serum magnesium level in the PCOS group was 1.58 ± 0.24 mg/dL, while in the control group it was 2.03 ± 0.19 mg/dL. This difference was statistically significant (p <0.001), suggesting a lower magnesium status in PCOS patients.

Further analysis revealed a moderate negative correlation between serum cortisol and magnesium levels (r = −0.46, p <0.001). This finding indicates that as cortisol levels increased, magnesium levels tended to decrease, suggesting a possible relationship between stress-related hormonal changes and magnesium deficiency in women with PCOS

Tables

Table 1: Baseline Characteristics

Parameter	PCOS (n=110)	Controls (n=110)	p-value
Age (years)	25.1 ± 4.1	24.6 ± 3.8	0.36
BMI (kg/m²)	27.8 ± 3.6	23.7 ± 2.9	<0.001
Waist Circumference (cm)	91.4 ± 7.8	80.2 ± 6.4	<0.001

Table 2: Comparison of Serum Cortisol Levels

Group	Mean Cortisol (µg/dL)	SD	p-value
PCOS	19.2	4.5	<0.001
Controls	13.1	3.2	

Table 3: Comparison of Serum Magnesium Levels

Group	Mean Magnesium (mg/dL)	SD	p-value
PCOS	1.58	0.24	<0.001
Controls	2.03	0.19	

Table 4: Correlation Between Cortisol and Magnesium

Parameter	r-value	p-value
Cortisol vs Magnesium	−0.46	<0.001

A significant negative correlation was observed between cortisol and magnesium levels.

Figures

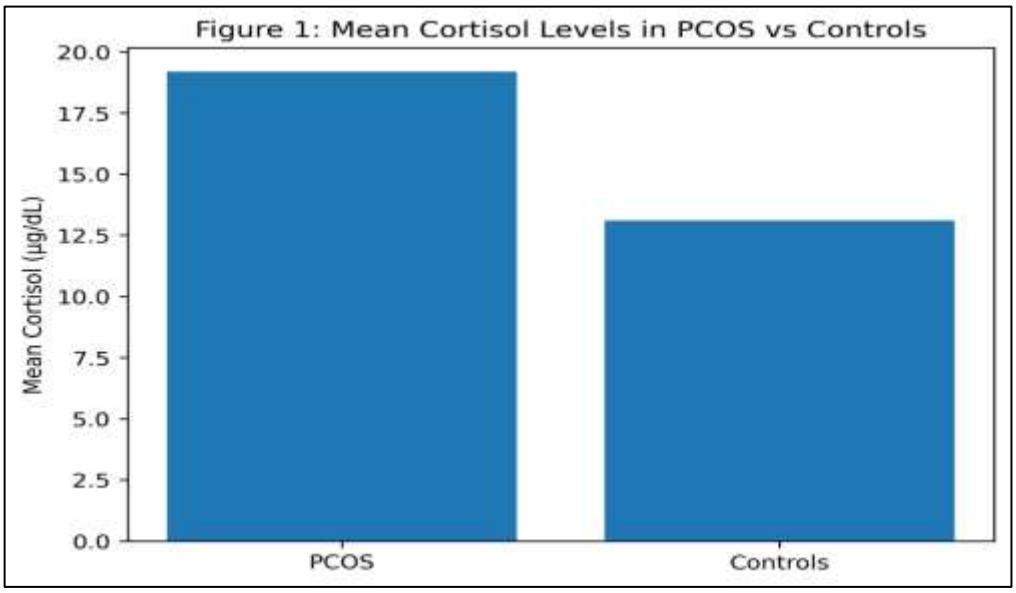

Figure 1. Bar graph showing mean cortisol levels in PCOS vs controls

PCOS: 19.2 µg/dl
Controls: 13.1 µg/dl

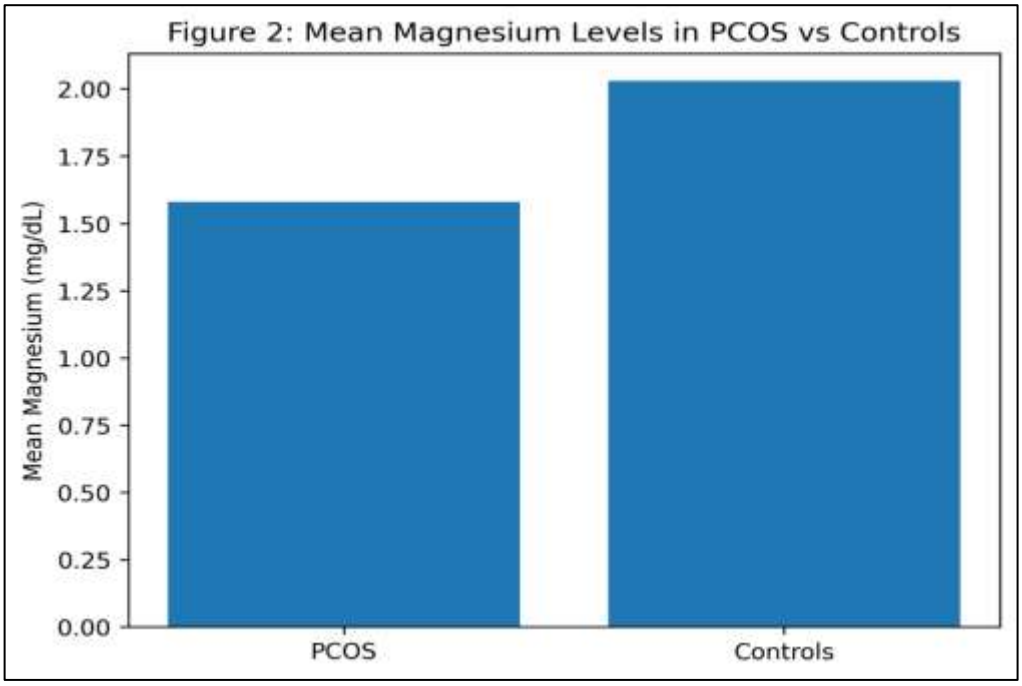

Figure 2. Bar graph showing mean magnesium levels

PCOS: 1.58 mg/dL
Controls: 2.03 mg/dL

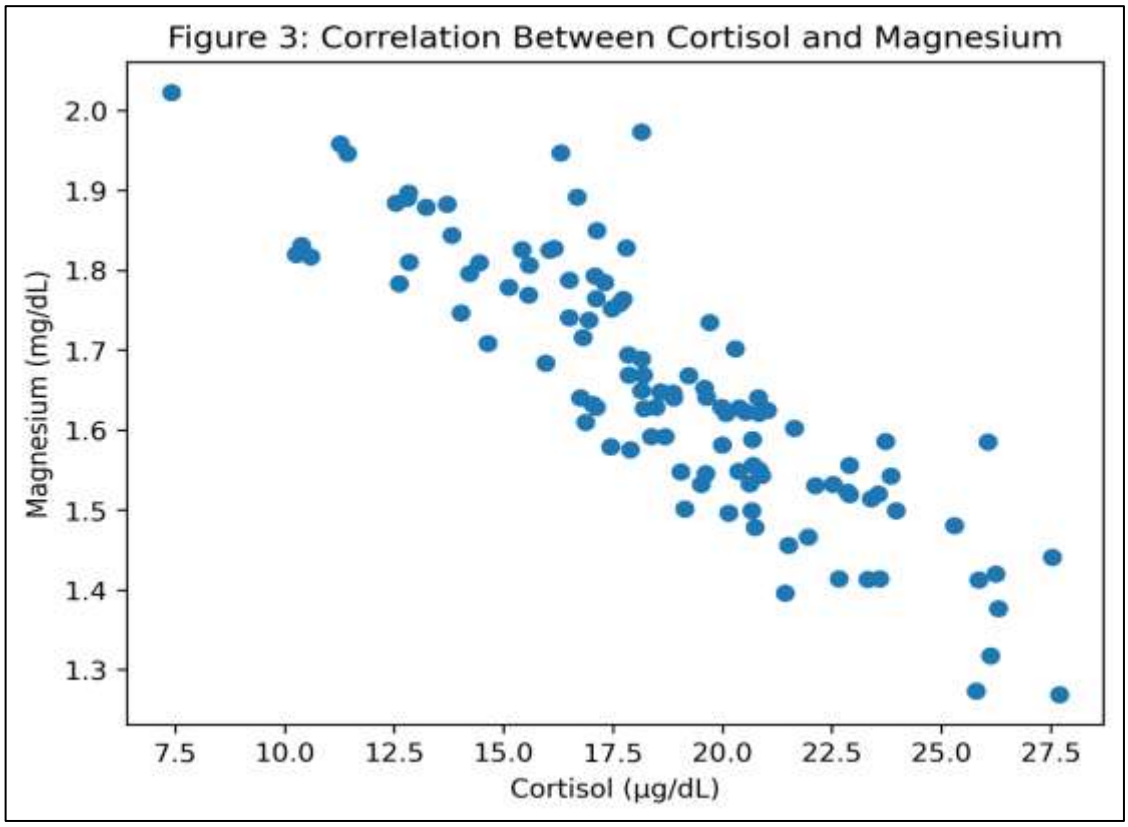

Figure 3. Scatter plot showing negative correlation between cortisol and magnesium levels

DISCUSSION

The present study evaluated serum cortisol and magnesium levels in women with PCOS and compared them with healthy controls.

The results demonstrated significantly higher cortisol levels in women with PCOS compared to controls. Elevated cortisol levels may indicate increased activation of the hypothalamic–pituitary–adrenal axis, which has been implicated in the pathophysiology of PCOS [8]. Increased cortisol secretion may contribute to insulin resistance, visceral fat accumulation, and metabolic dysfunction observed in PCOS patients [9].

Similarly, our findings showed significantly lower magnesium levels in PCOS patients compared to healthy controls. Magnesium plays a vital role in insulin receptor activity and glucose metabolism, and deficiency of this mineral may

worsen insulin resistance and metabolic disturbances [10]. Previous studies have also reported reduced magnesium levels in women with PCOS, suggesting that magnesium deficiency may be a common metabolic abnormality in this condition [11].

The present study also observed a moderate negative correlation between cortisol and magnesium levels, indicating that higher cortisol levels were associated with lower magnesium concentrations. This relationship may be explained by the fact that chronic stress and elevated cortisol can increase renal magnesium excretion, leading to magnesium depletion [12].

These findings are consistent with earlier studies that reported hormonal imbalance and micronutrient deficiencies in PCOS [6,11]. Magnesium supplementation has been shown to improve insulin sensitivity, inflammatory markers, and metabolic parameters in PCOS patients [13].

Therefore, monitoring cortisol and magnesium levels may help in better understanding the metabolic disturbances associated with PCOS and could potentially aid in the development of therapeutic strategies aimed at improving metabolic outcomes in affected women.

Limitations

- Single-center study
- Dietary magnesium intake not assessed
- Other metabolic markers such as insulin and HOMA-IR were not included

CONCLUSION

The present study demonstrates that women with PCOS have significantly higher serum cortisol levels and lower magnesium levels compared with healthy controls. These findings suggest that stress-related hormonal imbalance and magnesium deficiency may contribute to metabolic disturbances associated with PCOS.

Further large-scale studies are required to evaluate the therapeutic potential of magnesium supplementation and stress management in PCOS.

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