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Comparison of Magnesium Status Using 24-h Urine Magnesium Content and Magnesium Fraction Excretion in PCOS with Non-PCOS Control Women: a Cross-sectional Study

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Abstract

Magnesium (Mg) is the second most frequent intracellular cation, having an important role in normal enzyme function and insulin secretion. Polycystic ovarian syndrome (PCOS) is the most prevalent endocrinopathy in women of reproductive age and often associated with insulin resistance. Two systematic reviews and meta-analyses have been conducted to compare mean serum Mg levels between PCOS and control groups. Both studies detected unexplained heterogeneity among input studies and the two conclusions contradict each other, while approximately 1% of total body Mg is present in extracellular fluid (ECF) and serum Mg level does not represent Mg status well. For the first time, we investigated magnesium renal fraction excretion (FEMg) and compared mean values between PCOS and non-PCOS control women. This study is a cross-sectional analysis conducted at an academic medical center. Forty-four women were included in the PCOS group based on the Rotterdam criteria and 50 non-PCOS women were included in the control group. Statistical analysis of the relationship between 24-h urinary Mg content and FEMg, and also physical and metabolic variables, was performed. Main outcome measurements are 24-h urinary Mg content and FEMg. Mean values of 24-h urinary Mg content and FEMg did not significantly differ between PCOS and control groups ($P=0.22$ and $P=0.24$, respectively). Also, serum Mg levels and Ca/Mg ratio were similar between the groups ($P=0.17$ and $P=0.26$, respectively). Our data suggested Mg status in the PCOS group was similar to the non-PCOS control group and both were not magnesium deficient. For further investigation, we recommend using FEMg for evaluating Mg status rather than serum Mg levels. Considering collection of background diet is helpful and desired for future studies.

Keywords Polycystic ovarian syndrome · PCOS · Magnesium renal fraction excretion · Serum Mg level · 24-h urinary Mg content · FEMg

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Introduction

Polycystic ovarian syndrome (PCOS) is the most prevalent cause of chronic anovulation with androgen excess. It affects 5–10% of women in reproductive age [1]. There is evidence that dietary magnesium (Mg) is inversely associated with obesity, type 2 diabetes mellitus, metabolic syndrome, and chronic hypertension [2–7]. So we were encouraged to investigate the role of magnesium status in PCOS as a metabolic disorder.

Mg is the major intracellular divalent cation. Intracellular magnesium forms a key complex with adenosine triphosphate (ATP) and is an important cofactor for a wide range of enzymes, transporters, and nucleic acids required for normal cellular function, replication, and energy metabolism [8]. Several studies have shown significant differences in serum Mg levels in PCOS women in comparison with the control group [9, 10], while there are several studies that found no significant difference [11–14]. Two systematic reviews and meta-analyses have been conducted in 2020 that investigated serum magnesium levels in PCOS and non-PCOS control groups. They proved unexplained heterogeneity among input studies and their conclusions contradict each other [15, 16]. While Mg is the second most frequent intracellular cation and serum Mg level does not reflect total body Mg status [8], for the first time, this study compared Mg status in PCOS women vs non-PCOS control using 24-h urinary Mg content and magnesium renal fraction excretion (FEMg) rather than serum Mg levels.

Material and Methods

This study was a cross-sectional study conducted at the Milad Infertility Clinic at Imam Reza Hospital, Mashhad University of Medical Sciences, Iran, during 2021. Forty-four PCOS and 50 control non-PCOS women were recruited from outpatients who visited the Milad Infertility Clinic. The study design was approved by local and national ethics committee. Ethical code is IR.MUMS.MEDICAL.REC.1398.541, registered on https://ethics.research.ac.ir/. The study has followed the Declaration of Helsinki guideline, and informed consent was given by all participants.

When the study was proposed, we decided to have participants fulfill the Food Frequency Questionnaire (FFQ), but when faced with the COVID-19 pandemic, we were expected to minimize the exposure, so FFQ was omitted. To conform dietary magnesium intake between PCOS and control groups, a 3-day wash out period was considered. Participants were asked not to consume magnesium-rich food such as cocoa derivatives, nuts, seafood, and green vegetables in this period then go to laboratory. We provided "Guide to 24-h urine collection" in papers and distributed to participants. We also instructed them verbally and answered any question they had about the urine collection process.

The Rotterdam criteria were the basis of PCOS diagnosis in the PCOS group. Each woman with PCOS met at least two of the following criteria:

1. hirsutism or hyperandrogenemia in the absence of alternative known cause
2. oligomenorrhea or dysfunctional uterine bleeding
3. polycystic ovaries on ultrasonography

Infertile women who did not have any of the exclusion criteria were included in the non-PCOS control group. Exclusion criteria were as follows:

1. Known causes of hyperandrogenism and chronic anovulation
2. Previous known endocrinopathies including diabetes mellitus, untreated thyroid abnormalities, or parathyroid abnormalities
3. Chronic hypertension or previous known cardiovascular disease
4. Chronic kidney disease or electrolyte abnormalities including hypokalemia or hypercalcemia
5. Pregnant or breastfeeding women
6. Consumption of drugs and toxins including corticosteroid, Mg-based antacids/cathartics, diuretics (loop, thiazide, osmotic), and ethanol within the past 3 months

Measurements

Variables and measuring methods are listed in Table 1. Anthropometric and clinical variables were asked and measured at the clinic, and then participants were referred to laboratory, received as a routine patient. The main outcomes are 24-h urine Mg content and FEMg. Body mass index (BMI) and age were potential confounders.

Statistical Analysis

The Kolmogorov–Smirnov test was used to define whether the sample drawn complies normal distribution or not. To compare continuous data, the independent *t*-test was used for normally distributed variables and the Mann–Whitney test for non-normally distributed ones. We used Pearson's correlation test for parametric and Spearman's rho test for non-parametric variables to find out if there is correlation between these parameters

Table 1 Variable characteristics and measuring methods

Variable	Measuring method	Unit	Variable type
Acanthosis nigricans	Clinician	Yes/No	Qualitative
Menstrual disorder	Clinician	Yes/No	Qualitative
Hirsutism	Clinician	Yes/No	Qualitative
Acne	Clinician	Yes/No	Qualitative
Systolic blood pressure	Analogue sphygmomanometer	mmHg	Quantitative (continuous)
Diastolic blood pressure	Analogue sphygmomanometer	mmHg	Quantitative (continuous)
BMI	Scales $\text{BMI} = \frac{W}{H^2}$	kg/M^2	Quantitative (continuous)
Age	Identification card	year	Quantitative (continuous)
Magnesium renal fraction excretion (FEMg)	$\text{FEMg} = \frac{\text{Mg (U)}\times\text{Cr (S)}}{\text{Mg (S)}\times\text{Cr (U)}} \times 100$	%	Quantitative (continuous)
25-OH vitamin D	Agilent 1260 (HPLC)	ng/mL	Quantitative (continuous)
24-h urine volume	Scaled container	mL/24 h	Quantitative (continuous)
24-h urine creatinine	BS-800 Chemistry analyser by Mindray (UK) Ltd Pars Azmoon kit	mg/24 h	Quantitative (continuous)
24-h urine magnesium	BS-800 Chemistry analyser by Mindray (UK) Ltd Pars Azmoon kit	mg/24 h	Quantitative (continuous)
Fasting blood glucose (FBS)	BS-800 Chemistry analyser by Mindray (UK) Ltd Pars Azmoon kit	mg/dL	Quantitative (continuous)
Serum creatinine	BS-800 Chemistry analyser by Mindray (UK) Ltd Pars Azmoon kit	mg/dL	Quantitative (continuous)
Serum calcium (total)	BS-800 Chemistry analyser by Mindray (UK) Ltd Pars Azmoon kit	mg/dL	Quantitative (continuous)
Albumin	BS-800 Chemistry analyser by Mindray (UK) Ltd Pars Azmoon kit	g/dL	Quantitative (continuous)
Serum magnesium	BS-800 Chemistry analyser by Mindray (UK) Ltd Pars Azmoon kit	mg/dL	Quantitative (continuous)
Serum potassium	Spectrophotometry	mEq/dL	Quantitative (continuous)
Ca/Mg ratio	Corrected Ca/Mg Corrected Ca (mg/dL) = measured Ca (mg/dL) + [4 − albumin (g/dL)]	mg/dL / mg/dL	Quantitative (continuous)

and magnesium measures. P value < 0.05 was regarded statistically significant for all calculations. The data are reported in accordance with STROBE guidelines (https://www.equator-network.org/reporting-guidelines/strobe/). SPSS 26 statistical software was used to perform all statistical analyses. The statistical variable used to compare the main measurable outcome and calculating sample size was the mean Mg content of 24-h urine sample for both PCOS and control groups.

Sample Size

There was no study investigating 24-h urinary Mg content in PCOS women, so we calculated sample size due to studies conducted on normal Chinese men and type 2 diabetes mellitus patients [17, 18]. Sample size was calculated by Eq. 1 considering type 1 error (α) of 0.05 and type 2 error (β) of 0.20 (power = 80%). We used 31.0 mg/24-h as the effect size (d) of 24-h urine Mg content and 51.7 mg/24 h as standard deviation (SD). With the assumptions, we calculated 44 cases that were required in each group.

$$n = \frac{\left(z_1 - \frac{a}{2} + z_1 - \beta\right)^2 \left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)^2} \quad (1)$$

Results

3All participants were infertile. All were received at the laboratory and provided a 24-h urine and one-time blood sample. PCOS and control groups were age-matched but BMI was significantly higher in the PCOS group ($P = 0.002$). Profile of anthropometric and laboratory characteristics of PCOS and control groups is presented in Table 2. Frequency of important clinical features is listed in Table 3. Serum Mg levels were similar between the groups (P value = 0.17).

Table 2 Characteristics of PCOS and control

Variable	Normal values	PCOS ($n=44$)		Control ($n=50$)		P value	Parametric/non-parametric
		Mean	95% CI	Mean	95% CI		
Age		30.86	28.98–32.74	33.06	31.49–34.63	0.07	Parametric
BMI	18.5–25.0	28.49	26.57–30.40	24.93	23.72–26.13	0.002	Non-parametric
Systolic blood pressure (SBP)	< 140	107.5	103.6–111.3	107.3	103.7–110.9	0.93	Parametric
Diastolic blood pressure (DBP)	< 90	74.8	72.2–77.4	71.0	67.7–74.2	0.089	Non-parametric
Fasting blood glucose (FBS)	< 100	97.48	94.46–100.50	97.84	95.82–99.86	0.83	Parametric
Serum creatinine	0.6–1.0	0.88	0.85–0.91	0.84	0.82–0.86	0.02	Non-parametric
Serum calcium (total)	8.5–10.2	9.20	9.06–9.34	9.14	9.03–9.25	0.58	Non-parametric
Albumin	3.4–5.4	4.60	4.54–4.65	4.50	4.44–4.57	0.033	Parametric
Serum magnesium	1.8–2.6	2.47	2.39–2.54	2.41	2.35–2.47	0.17	Non-parametric
Serum potassium	3.5–5.5	4.12	4.04–4.19	3.98	3.91–4.05	0.007	Non-parametric
24-h urine volume	800–2000	1240	1084–1397	1309	1174–1443	0.38	Non-parametric
24-h urine creatinine	500–2000	898	832–964	885	822–949	0.77	Parametric
24-h urine magnesium	24–255	65.22	58.11–72.33	71.07	64.66–77.47	0.22	Parametric
Fraction excretion of magnesium (FEMg)	> 0.5%	2.661	2.401–2.921	2.881	2.607–3.155	0.24	Parametric
25-hydroxy vitamin D	> 30	26.1	21.7–30.6	23.5	19.4–27.5	0.41	Non-parametric
Ca/Mg ratio		3.55	3.44–3.66	3.64	3.53–3.74	0.26	Parametric

There was no significant difference in 24-h urinary Mg content (P value = 0.22) and FEMg (P value = 0.24) between the PCOS and control groups.

In medical practice, many clinicians request 24-h urine creatinine to check if urine collection is acceptable. The acceptable range is 500–2000 mg. We did not exclude any participants because of unacceptable urine collection. There were 2 participants with 24-h urine creatinine less than 500 mg, one 440 mg and the other 335 mg, both in the PCOS group. Urine volumes were respectively 1100 mL and 650 mL. No participant had urine creatinine more than 2000 mg.

Discussion

The results of this study demonstrate similar magnesium status between PCOS and non-PCOS control groups. No significant difference was seen in 24-h urinary Mg content or FEMg between PCOS and control groups ($P = 0.22$ and $P = 0.24$, respectively). Also, serum magnesium level was similar between the groups ($P = 0.17$).

Table 3 Frequency of clinical features

Clinical feature	PCOS ($n=44$)	Control ($n=50$)
Hirsutism	34 (77%)	8 (16%)
Acne	21 (47%)	11 (22%)
Acanthosis nigricans	14 (31%)	0 (0%)
Menstrual disturbance	37 (84%)	0 (0%)

Ca/Mg ratio was calculated by dividing the corrected Ca by the Mg: corrected Ca (mg/dL) = measured Ca (mg/dL) + [4 − albumin (g/dL)]. There was no significant difference among the groups (P value = 0.26).

PCOS is considered a heterogeneous disorder with multifactorial causes. Pathophysiology of PCOS is complex and incompletely understood. During the reproductive years, PCOS is associated with important reproductive morbidity, including infertility, irregular uterine bleeding, and increased pregnancy loss [1].

PCOS is a metabolic disorder and in many cases will be associated with diabetes mellitus, chronic hypertension, and metabolic syndrome. It is evident that dietary Mg is inversely associated with obesity, type 2 diabetes mellitus, metabolic syndrome, and chronic hypertension [2–7]. Intracellular magnesium is crucial for normal energy metabolism, as a cofactor for ATP and numerous enzymes and transporters, which is reflected in the rather global clinical effects that accompany disorders of magnesium homeostasis [19].

In a systematic review and meta-analysis, Babapour et al. focused on 8 studies and proved serum Mg level is lower in PCOS women than the control group (WMD, 95% CI; − 0.09 (− 0.17, − 0.02) mmol/L; $P = 0.01$). Also, they detected significant heterogeneity among the studies ($I^2 = 98.0\%$, $P < 0.001$). They classified studies based on BMI classes but they did not detect the source of heterogeneity. They observed significant differences in the pooled effect sizes of Mg concentration between PCOS and control groups in the studies conducted on overweight or obese women (− 0.07 (− 0.14, − 0.01) mmol/L; $P = 0.02$). They observed

no difference in Mg concentration between the groups in the subgroup of normal BMI (−0.11 (−0.25, 0.04) mmol/L; $P=0.14$) [16].

In another systematic review and meta-analysis, Yin et al. focused on 7 studies. They detected no significant difference in serum Mg levels between PCOS and control groups (SMD = −0.40, 95% CI: −1.04 to 0.23). Again, significant levels of heterogeneity were detected ($I^2=97\%$). They observed serum Mg was not significantly different between PCOS patients and healthy controls, irrespective of whether or not PCOS women were obese (overweight/obese: SMD = −1.05, 95% CI: −2.47 to 0.37; normal weight: SMD = −1.11, 95% CI: −3.24 to 1.02) [15].

Mg is an intracellular cation and serum levels may not reflect body Mg status well. According to Al-Ghamdi et al., a decrease of 24-h Mg excretion less than 12 mg is convincing evidence of magnesium deficiency for individuals. Also stated, FEMg > 0.5% or more than 24 mg in 24-h urine rules out magnesium deficiency [20]. For calculating fractional excretion of magnesium, both serum magnesium and 24-h urinary magnesium are considered. Serum magnesium concentration reflects intestinal magnesium absorption; fractional excretion of magnesium can be useful even if dietary magnesium is not measured. It can be an appropriate stand-alone indicator for magnesium status according to Al-Ghamdi et al.

Hypothetically, the heterogeneity observed in both systematic reviews and meta-analyses conducted on serum Mg levels may reveal the fact that serum Mg does not reflect magnesium status. For further investigation, we recommend using FEMg for evaluating Mg status rather than serum Mg levels.

Mg absorption was found to be normal or minimally reduced in vitamin D–deficient patients and vitamin D repletion resulted in a small, although significant increase in magnesium absorption, while overall balance was not affected due to increased urinary magnesium excretion. In our study [20], vitamin D mean values were similar between the PCOS and control groups (P value = 0.41).

Serum creatinine was significantly different between PCOS and control groups (P value = 0.02), and also serum potassium and albumin (respectively $P=0.007$ and $P=0.033$). One of the important reasons we measured these three parameters was to check similarity between PCOS and control groups, to find out if the groups are comparable or not. We used Pearson's correlation test for parametric and Spearman's rho test for non-parametric variables to find out if there is correlation between these parameters and magnesium measures. The results are listed in Table 4.

It is known that serum calcium is correlated with albumin. We observed it in our study. But there was no correlation between these three statistically significant parameters and magnesium measures. Ideally, we desire a control group with similar mean levels of albumin, serum creatinine, and serum potassium. Results of this study and variables we measured can be material of a bigger systematic review and meta-analysis.

Table 4 Correlation between magnesium measures and statistically significant parameters (P values)

	Serum potassium	Albumin	Ser Cr
Serum Mg	0.15	0.58	0.30
24-h urine Mg	0.80	0.70	0.15
FEMg	0.98	0.66	0.52
Serum Ca	0.019	0.000	0.003
Ca/Mg ratio	0.51	0.41	0.51

It is known that hypomagnesemia will affect PTH receptor sensitivity and cause resistant hypokalemia and hypocalcemia. This effect happens at low levels of magnesium status when it is symptomatic. Although differences in serum creatinine, serum potassium, and albumin are statistically significant between PCOS and control groups, it does not mean that it has clinical importance.

In the present study, BMI was significantly higher in the PCOS group ($P=0.002$). Sample size was not large enough for linear regression to assess BMI effect as a confounder. All participants were infertile; the fact should be considered while evaluating external validity of the research.

Conclusion

Our study suggested Mg status in the PCOS group was similar to the non-PCOS control group, and both were not Mg deficient. There was no clue of magnesium deficiency so the hypothesis comes to mind which use of Mg supplements would not be helpful in PCOS especially infertile PCOS women as well as infertile non-PCOS women.

For further investigation, we recommend using FEMg for evaluating Mg status rather than serum Mg levels. Also, considering collection of background diet is helpful and desired for future studies.

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Author Contribution SA, MM, MDM, and MN contributed to the conception and design. SA, MM, SHMV, MA, and NJ contributed to sampling and clinical part of the study. SA and MDM contributed to statistical analysis. SA drafted the manuscript. MM supervised the study.

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Data Availability Related data and the analyzed file have been attached and sent.

Declarations

Ethics Approval This was a cross-sectional study registered on https://research.mums.ac.ir/general/homePage.action website on 10/23/2019 with research code 980229. Ethical code is IR.MUMS.MEDICAL.REC.1398.541, registered on 8/13/2019 and accessible on https://ethics.research.ac.ir/ which is national ethics committee's website. This study has followed the Declaration of Helsinki guideline, and informed consent was given by all participants.

Competing Interests The authors declare no competing interests.

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