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Lifestyle Factors and Soluble RAGE in Women with Polycystic Ovary Syndrome Undergoing IVF: Associations with Micronutrient Intake and Physical Activity

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Research Article

Keywords:

Posted Date: September 29th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10346070/v1

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Additional Declarations: No competing interests reported.

Abstract

Background:

Advanced glycation end products (AGEs) contribute to the pathophysiology of polycystic ovary syndrome (PCOS) through activation of the AGE–RAGE pathway. Soluble RAGE (sRAGE), a circulating decoy receptor with anti-inflammatory properties, may be influenced by dietary factors and physical activity. This study investigated the associations of micronutrient intake and physical activity with serum and follicular fluid sRAGE levels in women with PCOS undergoing in vitro fertilization (IVF).

Methods:

In this case–control study, 44 women undergoing IVF (18 with PCOS and 26 controls) were enrolled. Dietary intake was assessed using a validated 168-item food frequency questionnaire, physical activity using a validated questionnaire, and serum and follicular fluid sRAGE concentrations by ELISA.

Results:

Women with PCOS consumed significantly lower amounts of several micronutrients than controls. Physical activity was not associated with serum or follicular fluid sRAGE. Although several micronutrients showed significant correlations with sRAGE, these associations were inconsistent between serum and follicular fluid.

Conclusion:

Women with PCOS had lower micronutrient intake than controls; however, these differences were not consistently reflected in sRAGE concentrations. These findings suggest that micronutrient intake alone may not explain alterations in sRAGE, and other factors involved in AGE–RAGE signaling may contribute to PCOS pathophysiology.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age, with an estimated prevalence of approximately 10–13%, depending on diagnostic criteria and population characteristics (1). PCOS is a heterogeneous disorder associated with reproductive, endocrine, and metabolic abnormalities, including ovulatory dysfunction, hyperandrogenism, insulin resistance, dyslipidemia, and impaired hypothalamic–pituitary–ovarian axis regulation (1). Increasing evidence also suggests that advanced glycation end products (AGEs) contribute to the pathophysiology of PCOS by promoting oxidative stress, chronic low-grade inflammation, and ovarian dysfunction (2, 3).

AGEs are formed through non-enzymatic reactions between reducing sugars and free amino groups of proteins, lipids, or nucleic acids, and may originate from both endogenous metabolism and exogenous sources, particularly diet and cigarette smoking (2, 4). Elevated AGE levels have been reported in the serum and follicular fluid of women with PCOS, suggesting a potential role for AGE accumulation in the ovarian microenvironment (2, 5). AGEs exert their biological effects mainly through binding to the receptor for advanced glycation end products (RAGE), which activates intracellular inflammatory and oxidative stress pathways and may further increase RAGE expression through a positive feedback mechanism (2, 6). In addition, AGEs may directly interact with extracellular matrix components, thereby contributing to altered tissue structure and function (2).

Soluble RAGE (sRAGE), which circulates in the bloodstream and is also detectable in follicular fluid, acts as a decoy receptor by binding AGEs and limiting their interaction with membrane-bound RAGE (2, 7). In PCOS, lower follicular fluid sRAGE levels have been reported and may reflect reduced protection against AGE–RAGE-mediated inflammation within the ovarian environment (2, 7). Experimental evidence also suggests that sRAGE may modulate vascular endothelial growth factor (VEGF)-related pathways in granulosa cells, supporting its potential protective role in follicular function (2). However, the relationship between sRAGE, ovarian reserve markers such as anti-Müllerian hormone (AMH), and reproductive outcomes remains insufficiently understood and may be influenced by age and follicular microenvironmental factors (8).

Lifestyle management, including healthy dietary habits and physical activity, is recommended as a core component of PCOS care to improve metabolic health, body composition, and overall wellbeing (1, 9). Dietary AGE intake may contribute to reproductive and metabolic disturbances in PCOS, while AGE-restricted dietary approaches have shown potential benefits for metabolic and hormonal parameters (10, 11). Moreover, AGE accumulation has been associated with reduced muscle performance and mobility, suggesting a possible link between AGE burden and lower physical activity capacity (12). Some micronutrients, particularly vitamin D, have also been linked to sRAGE regulation and AGE-related inflammatory pathways in women with PCOS (13).

Despite growing evidence regarding the AGE–RAGE axis in PCOS, the relationship between overall micronutrient intake, physical activity, and sRAGE levels in both serum and follicular fluid remains poorly investigated. Therefore, this study aimed to compare micronutrient intake and physical activity between women with and without PCOS and to evaluate their associations with serum and follicular fluid sRAGE levels.

Materials and Methods

Study Design and Participants

This case–control study was conducted among women undergoing in vitro fertilization (IVF) treatment at Erfan and Arash Hospitals, Tehran, Iran, between September 2024 and September 2025. The study

protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (Approval No. IR.TUMS.MEDICINE.REC.1401.066), and written informed consent was obtained from all participants before enrollment.

A total of 44 women undergoing IVF treatment were enrolled in the study, including 18 women with polycystic ovary syndrome (PCOS) and 26 women without PCOS who served as the control group.

Women were assigned to the PCOS group if they had a confirmed diagnosis of PCOS established by an experienced gynecologist based on comprehensive clinical evaluation and routine diagnostic procedures. Women in the control group underwent gynecological evaluation and had no clinical diagnosis or evidence suggestive of PCOS. In addition, they had no history of diabetes mellitus, thyroid disorders, chronic inflammatory diseases, abnormal uterine bleeding, chronic pelvic pain, or other major systemic diseases that could affect the study outcomes.

Eligibility Criteria

Women aged 20–45 years who were candidates for IVF treatment were eligible for inclusion. Participants with chronic systemic diseases, endocrine disorders other than PCOS, or medical conditions that could influence inflammatory or metabolic status were excluded. Women receiving medications known to affect metabolic or inflammatory parameters were also excluded.

Controlled Ovarian Stimulation and Sample Collection

All participants underwent controlled ovarian stimulation (COS) according to the routine IVF protocol used at the participating infertility centers. Pituitary suppression was achieved using a gonadotropin-releasing hormone (GnRH) antagonist protocol. Ovarian stimulation was initiated with daily subcutaneous injections of recombinant follicle-stimulating hormone (GONAL-f®, 150 IU; Merck, Germany) from the third to the fifth day of the menstrual cycle. Follicular development was monitored by serial transvaginal ultrasonography. When at least two follicles reached a diameter of 15–17 mm, final oocyte maturation was induced by administration of recombinant human chorionic gonadotropin (hCG; Ovitrelle®, Merck, Germany). Transvaginal ultrasound-guided oocyte retrieval was performed approximately 34–36 hours after hCG administration.

Follicular fluid (FF) was collected from the first mature follicle aspirated while carefully avoiding visible blood contamination. Samples were centrifuged at 15,000 × g for 5 minutes, and the supernatant was aliquoted and stored at − 80°C until analysis.

Peripheral venous blood samples were collected on the day of oocyte retrieval in plain tubes without anticoagulants. Following clot formation at room temperature for 15–30 minutes, samples were centrifuged at 2,000 × g for 10 minutes at 4°C. Serum aliquots were stored at − 80°C until measurement of soluble receptor for advanced glycation end products (sRAGE)

Physical Activity Assessment

Physical activity was assessed using a structured interviewer-administered questionnaire completed by a trained nutritionist. The questionnaire consisted of nine domains representing habitual daily activities, including sleep and rest, sedentary behaviors, computer use, standing activities, household tasks, walking, stair climbing, recreational cycling, carrying light loads, gardening, aerobic exercise, running, volleyball, and other sports activities. Participants reported the average duration of each activity in hours and minutes. (14)

The collected data were used to classify participants according to their level of physical activity for subsequent statistical analysis.

Dietary Assessment

Dietary intake was assessed using a validated semi-quantitative 168-item Food Frequency Questionnaire (FFQ), which was completed during the participants' first study visit to assess their habitual dietary intake over the previous year. The questionnaire was administered by an experienced nutritionist through face-to-face interviews. Participants reported the frequency of consumption of each food item on a daily, weekly, or monthly basis, and portion sizes were estimated using standard household measures and converted into grams.

Dietary data were entered and analyzed using the nutrient analysis software routinely employed by the nutrition research team. Daily energy intake, macronutrient intake, and micronutrient intake were estimated based on the USDA Food Composition Tables (FCT). (15) The calculated dietary variables were subsequently used for statistical analyses.

Measurement of Serum and Follicular Fluid sRAGE

Serum and follicular fluid (FF) concentrations of soluble receptor for advanced glycation end products (sRAGE) were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions. All samples were analyzed in duplicate, and the average value was used for statistical analysis. Absorbance was measured using a microplate reader at the recommended wavelength, and sRAGE concentrations were calculated from a standard calibration curve. Serum and FF samples were analyzed under identical laboratory conditions to minimize analytical variability.

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics version 28 and GraphPad Prism software 9.5.1. Descriptive statistics were expressed as median with interquartile ranges (25th–75th percentiles) or mean ± standard deviation (SD). Normality was assessed using the Shapiro-Wilk test. For comparisons between two independent groups (PCOS vs. Non-PCOS), the Mann-Whitney U test was

employed due to non-normal data distribution. For comparisons across more than two groups (e.g., physical activity levels: low, moderate, high), the Kruskal-Wallis test was applied, followed by Dunn's post-hoc test adjusted with Bonferroni corrections. Physical activity levels (PA) were categorized into low, moderate, and high. Spearman's correlation coefficients were calculated to assess relationships between biochemical markers (serum sRAGE, FFsRAGE) and nutritional variables (age, BMI, PA, and dietary nutrient intake). Post-hoc power analysis for the Mann-Whitney U test indicated that the study had sufficient power (> 80%) to detect differences in nutrient intake between the groups. All findings were deemed statistically significant at $p < 0.05$.

Results

Participant Characteristics A total of 44 women undergoing IVF were included in the study, consisting of 18 women with PCOS and 26 women without PCOS. Baseline characteristics of the study groups are presented in Table 1. Women with PCOS were significantly younger than controls [33 (26.75–37.25) vs. 40 (35–42.5) years, P = 0.002]. No significant differences were observed between the groups in BMI, physical activity level, serum sRAGE, or follicular fluid sRAGE concentrations.

Table 1
summarizes anthropometric and physical activity variables between the two groups.

Variable	**PCOS (n = 18) Median (IQR)**	**Non-PCOS (n = 26) Median (IQR)**	**Mann-Whitney U | $\varvec{\chi^2}$**	**p-value**
Age (Years)	33 (26.75–37.25)	40 (35–42.5)	109	0.002*
BMI (Body Mass Index, kg/m²)	26.5 (22–30)	24.5 (22–27)	190	0.292
Physical Activity (PA MET/h/d)				
Low PA (%)	38.8%	34.6%	5.055	0.093
Moderate PA (%)	16.6%	46.1%		
High PA (%)	44.4%	19.2%		
Serum sRAGE	3.35(1.375–3.95)	3.5(1.45–3.8)	228	0.886
FF sRAGE	4.15(3.125–4.225)	3.9(3.175–4.025)	163.5	0.091

0.093), or total energy intake (p = 0.294). (Table 1, Fig. 1).

Nutritional Intake Differences

Median dietary intakes of energy, macronutrients, and micronutrients were compared between women with PCOS and controls (Table 2). Total energy intake and macronutrient consumption did not differ

significantly between the two groups. However, women with PCOS had significantly lower intakes of several micronutrients than controls. Significant differences were observed for sodium, iron, calcium, copper, manganese, selenium, fluoride, chromium, potassium, iodine, vitamin A, and vitamin E ($P < 0.05$ for all). No significant differences were found for the remaining dietary variables.

Table 2
Nutritional Information of the PCOS + NON PCOS groups

sodium (mg)	**PCO**	**Non PCOS**	**Man**	**p-value**
	N = 18	**N = 26**	**Whitney U**	
	Median(IQR)	**Median(IQR)**		
	1466.(787.0-3229.)	**2755.(1776.-3731.)**	**144**	**0.032**
Iron(mg)	332.3(171.8-508.1)	801.7(497.7–1416.)	83	0.000*
Calcium(mg)	2111.(729.7–3865.)	4709.(2160.-8530.)	121	0.006*
Copper(µg)	1433.(1035.-3578.)	3214.(1589–4891.)	125	0.009*
Mn (Manganum) (mg)	103.9(63.68–130.3)	186.1(112.8-367.2)	107	0.002*
Selenium(µg)	571.5(175.4-872.9)	972.6(737.7–1805.)	102	0.001*
Fluoride(mg)	12.17(7.2-37.88)	36.15(14.37–54.58)	127	0.009*
Chromium(µg)	32.5(32.26–32.9)	33.39(32.81–34.31)	113	0.003*
K(Potassium) (mg)	2228.(1301.-2878.)	4216.(2669.-6967.)	91	0.000*
Iodine(µg)	12.82(11.43–16.52)	18.39(14.91–22.75)	102	0.002*
Phosphorus(mg)	772.7(363.3–2808.)	2122.(904.3–4478)	158	0.070
Zinc(mg)	134.1(116.1-196.6)	237.1(80.44–507.8)	178	0.181
Vitamin A (µg)	3.19(2.51–6.272)	8.53(5.175–14.9)	63	0.000*
Vitamin E(mg)	3.175(2.672–3.53)	3.845(3.097–5.067)	123.5	0.008
Vitamin C(mg)	967.5(673.1–1034.)	929.8(196.6–1181.)	221	0.756
Vitamin D(µg)	0.11(0.03–0.402)	0.06(0.04–0.132)	166	0.103
α-tocopherol(mg)	19.77(11.88–25.12)	16.33(12.25–24.47)	231	0.943
Vitamin B12(µg)	2.39(1.697–3.262)	2.905(2.36–3.832)	164.5	0.097
Vitamin B2(mg)	343.2(279.5-572.1)	448.6(321.4-647.1)	191	0.305
vitamin B3(m)	384.8(329.1-573.4)	493.3(317.8-629.1)	200	0.417
Vitamin.B6(mg)	1.915(1.2-2.982)	3.105(1.68–4.845)	164	0.095
Total.Folate(µg)	19.42(14.08–34.16)	27.58(17.89–43.24)	176	0.166
Vitamin.B12(µg)	127.4(22.89–360.9)	275.3(60.17–504.3)	184	0.233

sodium (mg)	PCO N = 18 Median(IQR)	Non PCOS N = 26 Median(IQR)	Man Whitney U	p-value
	1466.(787.0-3229.)	**2755.(1776.-3731.)**	**144**	**0.032**
Vitamin B7(mg)	906.7(572.9–1475.)	1048.(776.8–1792.)	205	0.489
Vitmin.k(µg)	285.2(155.1-548.2)	326.7(211.5-541.5)	214	0.633
B Carotene (µg)	8.905(5.882–13.72)	8.395(6.737–14.33)	225	0.830
A Carotene (µg)	1.315(0.827–2.252)	1.315(0.932–2.472)	212	0.599
Lutein(µg)	4.785(2.462–13.39)	5.6(3.752–8.935)	231	0.943
Lycopene(µg)	79.81(52.56–161.1)	73.53(54.69–115.3)	203	0.459
Caffeine(mg)	52.14(50.54,62.5)	50(1.175,63.61)	170.5	0.129
Kcal(Kilo Calorie)	1629.(1174.,1940.)	1840.(1300.,2869.)	190	0.294

*Significance at $P < 0.05$.

Associations Between Dietary Micronutrients and sRAGE Levels

The associations between dietary micronutrient intake and sRAGE concentrations in serum and follicular fluid were evaluated separately in women with PCOS and controls (Tables 3 and 4).

In women with PCOS, significant inverse correlations were observed between follicular fluid sRAGE concentrations and dietary intakes of vitamin B6, niacin (vitamin B3), and folate. In addition, serum sRAGE concentrations showed significant negative correlations with zinc, folate, and α-carotene intake, whereas positive correlations were identified with chromium and vitamin A intake.

In the control group, no consistent pattern of significant associations was observed between dietary micronutrient intake and serum or follicular fluid sRAGE concentrations.

Table 3
Spearman's correlation coefficients between biomarkers and variables in the entire population, PCOS and NON PCOS groups.

	FF SRAGE		SERUM SRAGE	
	r	P value	r	P value
Age	-0.330	0.029*	0.130	0.401
BMI (Body Mass Index)	0.506	0.001*	0.019	0.902
Physical Activity	0.048	0.756	0.232	0.129
Kcal(Kilo Calorie)	-0.144	0.352	0.061	0.693
Total Fiber	-0.177	0.250	0.004	0.979
Caffeine(mg)	0.190	0.216	0.035	0.821
Vitamin. A (µg)	-0.044	0.779	0.093	0.550
Vitamin. E(mg)	0.037	0.812	0.141	0.360
Vitamin. C(mg)	0.015	0.922	0.002	0.990
Vitamin. D(µg)	-0.027	0.864	-0.337	0.026*
Phosphorus(mg)	-0.213	0.165	0.116	0.455
Zinc(mg)	-0.217	0.158	0.009	0.956
α-tocopherol(mg)	-0.098	0.528	0.125	0.419
Vitamin B12(µg)	-0.055	0.725	0.152	0.326
Vitamin B2(mg)	-0.088	0.570	0.071	0.646
vitamin B3(m)	-0.045	0.773	0.080	0.608
Vitamin.B6(mg)	-0.123	0.427	0.120	0.438
Total.Folate(µg)	-0.245	0.109	0.053	0.734
Vitamin.B12(µg)	-0.156	0.311	0.199	0.197
Vitamin B7(mg)	-0.159	0.301	0.111	0.472
Vitmin.k(µg)	-0.204	0.184	0.049	0.753
B Carotene (µg)	-0.197	0.200	0.081	0.599
A Carotene (µg)	-0.168	0.276	-0.055	0.724
Lutein(µg)	-0.106	0.492	0.070	0.651

	FF SRAGE		SERUM SRAGE	
	r	**P value**	**r**	**P value**
Lycopene(µg)	-0.074	0.631	0.050	0.746
caffeine(mg)	0.19	0.216	0.035	0.821
Kcal(Kilo Calorie)	**-0.144**	**0.352**	**0.061**	**0.693**

Statistical significance using the spearman correlation coefficient. *Significance at P < 0.05.

In the PCOS group, FFsRAGE demonstrated negative correlations with vitamin B3 (r = -0.536, p = 0.022) and vitamin B6 (r = -0.572, p = 0.013). Serum sRAGE levels correlated positively with selenium (r = 0.476, p = 0.046) and negatively with zinc (r = -0.528, p = 0.024), potassium (r = 0.476, p = 0.046), a Carotene (r=-0.562, p = 0.015) (Table 4).

Table 4
Spearman Correlation Coefficients Between Biomarkers and Nutritional Variables in PCOS Group

PCOS	FFsRAGE		Serum sRAGE	
	r	P (two-tailed)	r	P (two-tailed)
Age	-0.113	0.655	0.076	0.765
BMI (Body Mass Index)	0.436	0.070	-0.088	0.727
Physical Activity	-0.110	0.665	0.073	0.772
Kcal(Kilo Calorie)	-0.409	0.092	-0.442	0.066
sodium (mg)	0.252	0.313	0.449	0.062
Iron(mg)	0.422	0.081	0.305	0.219
Calcium(mg)	0.083	0.745	0.126	0.618
Copper(µg)	0.379	0.121	0.369	0.132
Mn (Manganum) (mg)	0.434	0.072	0.430	0.075
Selenium(µg)	0.228	0.363	0.476	0.046*
Fluoride(mg)	0.411	0.090	0.402	0.098
Chromium(µg)	0.047	0.853	0.277	0.266
K(Potassium) (mg)	0.374	0.126	0.476	0.046*
Iodine(µg)	0.438	0.069	0.280	0.261
Vitamin. A (µg)	-0.376	0.125	-0.440	0.068
Vitamin. E(mg)	-0.004	0.987	-0.440	0.068
Vitamin. C(mg)	-0.221	0.379	-0.392	0.108
Vitamin. D(µg)	-0.453	0.059	-0.213	0.397
Phosphorus(mg)	-0.361	0.142	-0.256	0.305
Zinc(mg)	-0.361	0.142	-0.528	0.024*
α-tocopherol(mg)	-0.358	0.144	-0.248	0.321
Vitamin B12(µg)	-0.074	0.770	-0.138	0.587
Vitamin B2(mg)	-0.438	0.069	-0.345	0.161
vitamin B3(m)	-0.536	0.022*	-0.303	0.222

PCOS	FFsRAGE		Serum sRAGE	
	r	P (two-tailed)	r	P (two-tailed)
Vitamin.B6(mg)	-0.572	0.013*	-0.284	0.254
Total.Folate(µg)	-0.413	0.089	-0.408	0.093
Vitamin.B12(µg)	-0.260	0.297	-0.086	0.735
Vitamin B7(mg)	-0.469	0.050	-0.410	0.091
Vitmin.k(µg)	-0.415	0.087	-0.388	0.112
B Carotene (µg)	-0.488	0.040*	-0.396	0.104
A Carotene (µg)	-0.431	0.074	-0.562	0.015*
Lutein(µg)	-0.260	0.297	-0.233	0.353
Lycopene(µg)	-0.338	0.171	-0.385	0.115
caffeine(mg)	-0.453	0.059	-0.213	0.397
Kcal(Kilo Calorie)	-0.409	0.092	-0.442	0.066

Statistical significance using the spearman correlation coefficient. *Significance at $P < 0.05$

In the non-PCOS group, FFsRAGE was inversely associated with BMI ($r = -0.465$, $p = 0.017$), vitamin B3 ($r = 0.402$, $p = 0.042$) while serum sRAGE showed positive correlations with vitamin B7 ($r = 0.441$, $p = 0.024$) (Table 5).

Table 5
Spearman Correlation Coefficients Between Biomarkers and Nutritional Variables in Non-PCOS Group

Non pcos	FFsRAGE		sRAGE	
	r	p-value	r	p-value
Age	-0.342	0.088	0.039	0.850
BMI (Body Mass Index)	0.465	0.017*	0.067	0.746
Physical Activity	0.170	0.407	0.387	0.051
sodium (mg)	-0.038	0.853	-0.080	0.699
Iron(mg)	-0.103	0.618	-0.120	0.561
Calcium(mg)	-0.206	0.313	-0.166	0.419
Copper(µg)	0.042	0.838	0.022	0.915
Mn (Manganum) (mg)	-0.150	0.466	-0.151	0.462
Selenium(µg)	-0.142	0.489	-0.052	0.801
Fluoride(mg)	-0.178	0.386	-0.127	0.537
Chromium(µg)	0.028	0.892	0.014	0.946
K(Potassium) (mg)	-0.167	0.415	-0.149	0.467
Iodine(µg)	-0.044	0.829	0.062	0.764
Vitamin. A (µg)	-0.021	0.920	-0.115	0.577
Vitamin. E(mg)	-0.109	0.595	0.068	0.743
Vitamin. C(mg)	0.311	0.122	0.206	0.314
Vitamin. D(µg)	-0.069	0.738	-0.268	0.186
Phosphorus(mg)	0.008	0.969	0.267	0.187
Zinc(mg)	-0.001	0.996	0.199	0.330
α-tocopherol(mg)	0.173	0.397	0.371	0.062
Vitamin B12(µg)	0.145	0.481	0.378	0.057
Vitamin B2(mg)	0.322	0.108	0.308	0.126
vitamin B3(m)	0.402	0.042*	0.289	0.152
Vitamin.B6(mg)	0.270	0.183	0.297	0.141
Total.Folate(µg)	0.063	0.760	0.361	0.070

Non pcos	FFsRAGE		sRAGE	
	r	p-value	r	p-value
Vitamin.B12(µg)	-0.017	0.933	0.326	0.105
Vitamin B7(mg)	0.197	0.335	0.441	0.024*
Vitmin.k(µg)	0.102	0.621	0.348	0.082
B Carotene (µg)	0.143	0.486	0.386	0.052
A Carotene (µg)	0.121	0.558	0.258	0.203
Lutein(µg)	0.092	0.654	0.273	0.178
Lycopene(µg)	0.241	0.237	0.329	0.101
caffeine(mg)	0.374	0.06	0.148	0.472
Kcal(Kilo Calorie)	0.173	0.398	0.265	0.191

Statistical significance using the spearman correlation coefficient. *Significance at P < 0.05

Association Between Physical Activity and sRAGE

Physical activity levels were categorized as low, moderate, and high. The associations between physical activity level and serum and follicular fluid sRAGE concentrations were evaluated in both the PCOS and control groups. No statistically significant associations were observed between physical activity level and sRAGE concentrations in either serum or follicular fluid (Tables 6–7) (Fig. 2).

Table 6
Serum sRAGE and FFsRAGE by Physical Activity Levels in PCOS Group

FF Serum RAGE	LOW	Moderate	High	p-value
	N = 16	N = 15	N = 13	
	4.1(0.94–4.2)	4.1(2.2–5.3)	4.2(3.425–4.275)	0.679
SERUM SRAGE	3.3(1.3–4.1)	2(0.56–3.4)	3.55(1.825–4.275)	0.458

*: The significance level is p < 0.05.

- Kruskal-Wallis test.

Table 7
Serum sRAGE and FFsRAGE by Physical Activity Levels in Non PCOS Group

FF SERUM RAGE	LOW	Moderate	High	p-value
	N = 16	**N = 15**	**N = 13**	
	3.85(3.175–4.175)	**3.9(3.1–4.1)**	**4.1(3.3–4.25)**	**0.326**
SERUM RAGE	3.5(1.325–3.875)	3.4(2-3.8)	3.4(1.35–3.9)	0.997

*: The significance level is $p < 0.05$.

- Kruskal-Wallis test.

Discussion

This study investigated the associations of micronutrient intake and physical activity with serum and follicular fluid sRAGE concentrations in women with PCOS undergoing IVF. The main findings were that women with PCOS had significantly lower intakes of several micronutrients compared with controls, whereas physical activity levels did not differ significantly between the groups. In addition, only a limited number of micronutrients showed significant correlations with serum or follicular fluid sRAGE concentrations, and these associations were not consistent across biological compartments. These findings suggest that the relationship between micronutrient intake and sRAGE in PCOS is complex and may not be explained by dietary micronutrient intake alone.

The present study demonstrated that women with PCOS consumed significantly lower amounts of several essential micronutrients than women without PCOS despite having comparable total energy intake and physical activity levels. This finding suggests that dietary quality, rather than overall energy intake, may differ between women with and without PCOS.

Collectively, these findings support our observation that inadequate micronutrient intake is common among women with PCOS and may contribute to the metabolic and reproductive abnormalities associated with this syndrome. Nevertheless, because of the case–control design of the present study, causal relationships cannot be established.

One of the most interesting findings of the present study was that only a limited number of micronutrients were significantly associated with serum and follicular fluid sRAGE concentrations. Moreover, both positive and negative correlations were observed, suggesting that the relationship between micronutrient intake and sRAGE regulation is more complex than initially anticipated.

Experimental and clinical evidence indicates that some micronutrients may influence the AGE–RAGE pathway. For example, vitamin D supplementation has been reported to increase circulating sRAGE concentrations while improving metabolic and reproductive outcomes in women with PCOS (23).

Likewise, vitamin C supplementation has been shown to reduce circulating AGEs and oxidative stress, supporting the concept that antioxidant nutrients may modulate AGE-related pathways (24).

Nevertheless, our findings suggest that micronutrient intake alone is unlikely to explain the observed variation in sRAGE concentrations. A long-term intervention comparing low-AGE and high-AGE diets demonstrated that reducing dietary AGE intake did not consistently increase circulating sRAGE concentrations, despite improvements in dietary quality (25) Similarly, previous studies have reported that circulating AGE levels are influenced not only by micronutrient intake but also by food processing, cooking methods, and dietary fat content, all of which affect endogenous AGE formation and absorption (26). Furthermore, Pearce et al. demonstrated that diets matched for energy and micronutrient content but differing in AGE content produced metabolic effects that could not be explained solely by differences in micronutrient intake (27)

Taken together, these findings support our observation that the association between dietary micronutrients and sRAGE is multifactorial. In women with PCOS, sRAGE concentrations are likely influenced by the interaction of dietary quality, AGE exposure, oxidative stress, and metabolic status rather than by individual micronutrients alone.

In contrast to micronutrient intake, physical activity was not significantly associated with serum or follicular fluid sRAGE concentrations in the present study. Although regular physical activity is considered a cornerstone of lifestyle management for women with PCOS because of its beneficial effects on insulin sensitivity, body composition, and reproductive function, its direct influence on circulating sRAGE concentrations remains unclear (28). Furthermore, recent systematic reviews indicate that exercise interventions improve metabolic and hormonal outcomes in women with PCOS; however, evidence regarding their effects on biomarkers of the AGE–RAGE pathway is still limited and inconsistent (29). Therefore, the absence of a significant association in the present study may reflect the multifactorial regulation of sRAGE, the use of questionnaire-based physical activity assessment, and the relatively small sample size rather than a true lack of biological effect.

Strengths and Limitations

The present study has several strengths. Notably, it is among the few studies to simultaneously evaluate dietary micronutrient intake, physical activity, and both serum and follicular fluid sRAGE concentrations in women with PCOS undergoing IVF. However, the relatively small sample size, the case–control design, and the use of self-reported questionnaires should be considered when interpreting the findings. In addition, inflammatory and oxidative stress biomarkers were not measured, limiting further mechanistic interpretation.

Conclusion

In conclusion, women with PCOS undergoing IVF exhibited lower dietary intakes of several essential micronutrients than women without PCOS. Although selected micronutrients were associated with

serum and follicular fluid sRAGE concentrations, these relationships were not consistent, suggesting that sRAGE regulation is influenced by multiple metabolic and inflammatory factors rather than dietary micronutrient intake alone. No significant association was observed between physical activity and sRAGE concentrations. These findings highlight the potential importance of dietary quality in women with PCOS and support the need for larger prospective studies to clarify the interactions between nutrition, lifestyle factors, and the AGE–RAGE pathway in reproductive health.

Abbreviations

sRAGE
soluble Receptor for Advanced Glycation End Product
AGE
Advanced Glycation End Product
FF
follicular fluid
PCOS
Polycystic Ovary Syndrome

Declarations

Declaration of Helsinki Statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (as revised in 2013). The research protocol was reviewed and approved by the Institutional Ethics Committee of Tehran University of Medical Science (Approval No: IR. TUMS.MEDICINE. REC.1401.066). All participants were fully informed about the study objectives and procedures, and written informed consent was obtained prior to enrollment. Participation was voluntary, and confidentiality of personal and clinical data was strictly maintained throughout the study

Ethics approval and consent to participate: The study was approved by the ethics committee of Tehran university of Medical Science (IR. TUMS.MEDICINE. REC.1401.066) and a written informed consent were taken from all participants.

Consent for publication: N/A

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

Funding: This project was a postdoc project of Dr. Neda Emami and supported by Department of Gynaecology and Obstetrics, Tehran University of Medical Sciences, Tehran, Iran.

Authors' contributions: NE: Supervision, data gathering, drafting of the manuscript and interpretation of data; AM: Study designing, supervision, :ZZ Statics analyses; and. All authors discussed the results, were participated in writing of first draft of the manuscript, and approved the last version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgments

We thank all participants who were involved in the present study. We also would like to extend our appreciation Royan Institute laboratory staffs and Shahrdari laboratory, especially Mr. Bigharaz for their sincere contributions in all laboratory procedures. Surgical teams in several hospitals are highly appreciated for their assistance in biopsy collection.

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Figures

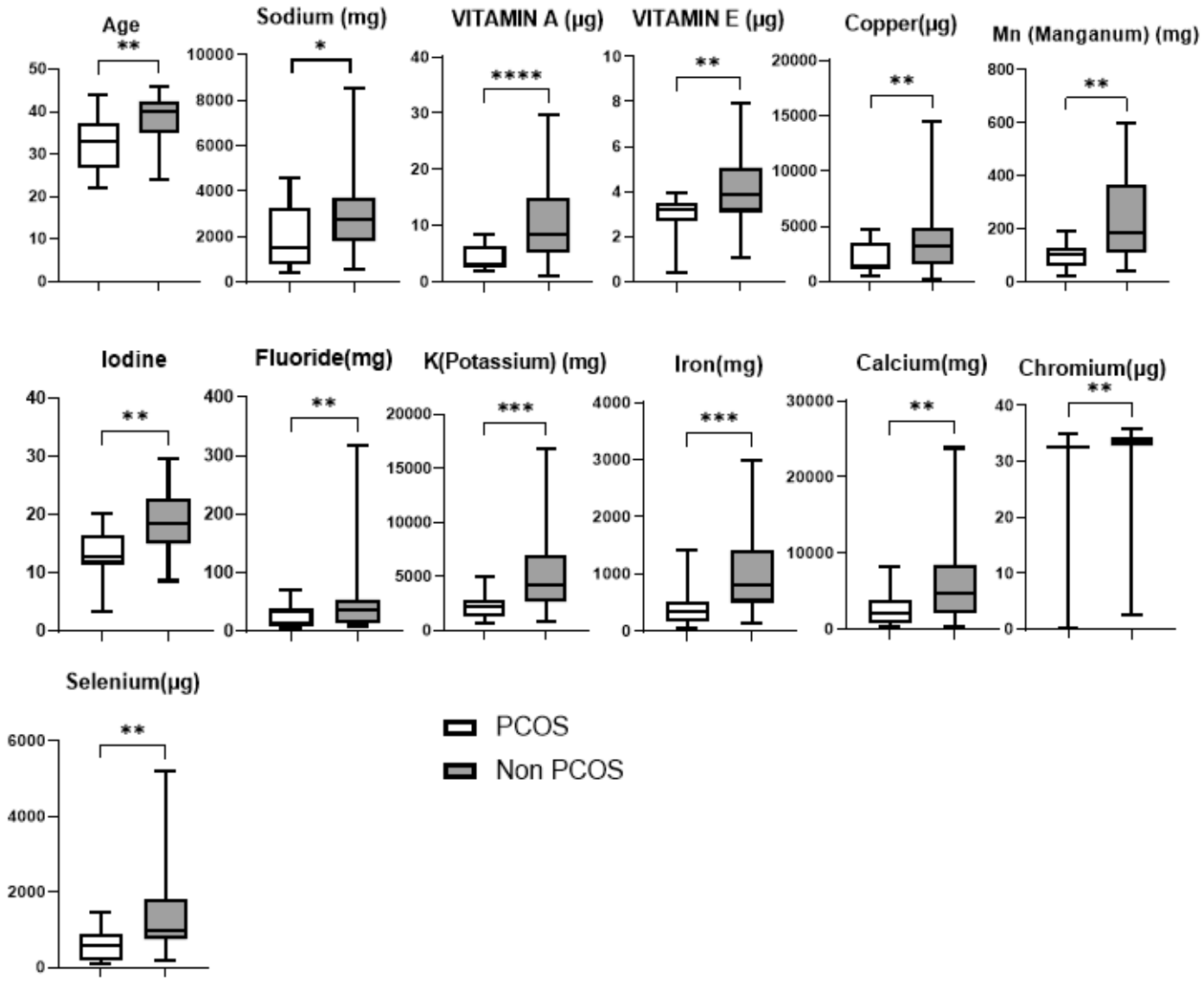

Figure 1

Shows the median (25%-75%) values of selected nutrients in the PCOS and Non PCOS groups. P-values are provided where concentrations were significantly different between groups. The significance level is p<0.05.

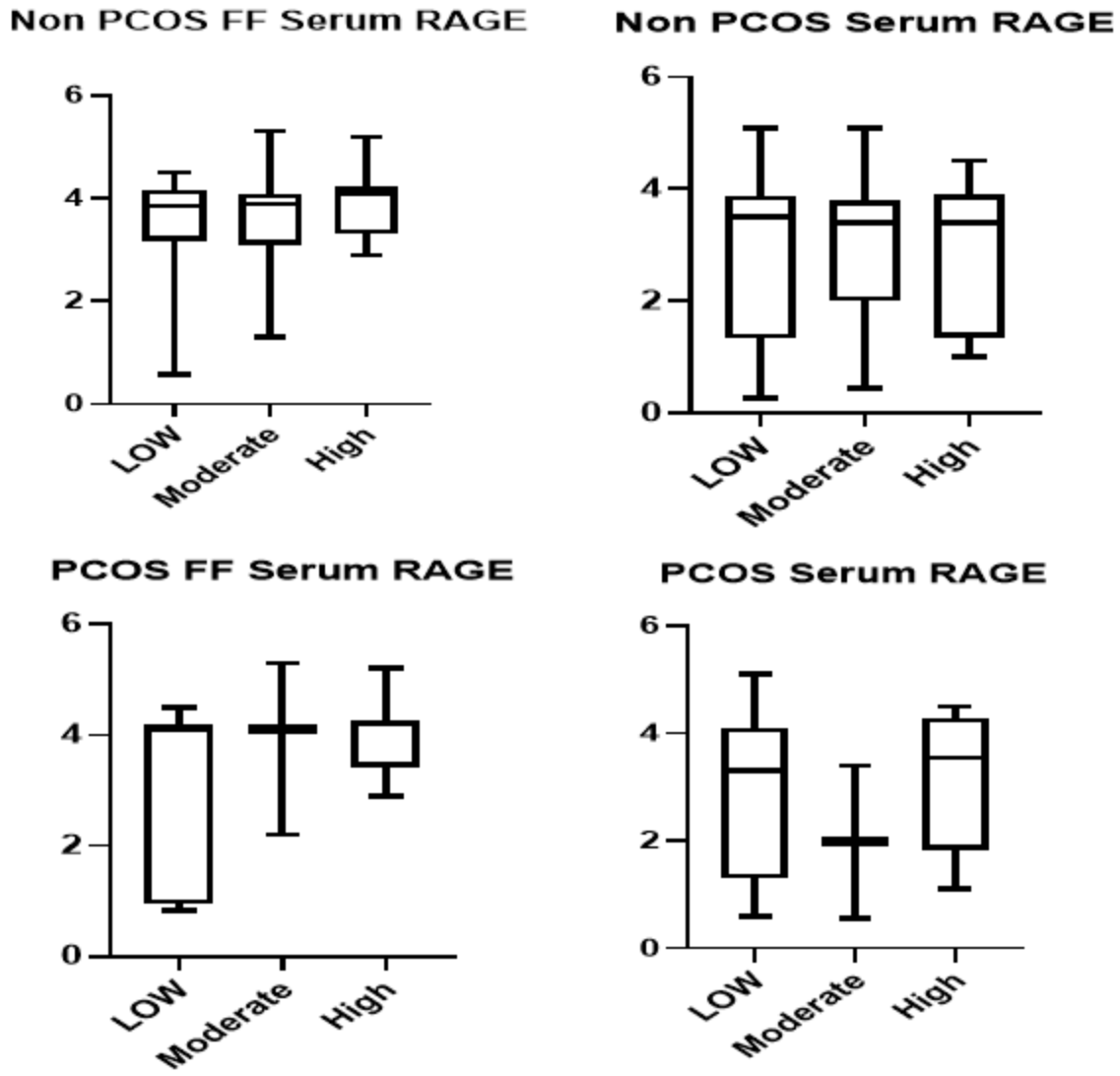

Figure 2

Median (25%–75%) of SERUM SRAGE and FF SRAGE in groups with low, moderate, or high PHYSICAL ACTIVITY. The significance level is p<0.05.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryPhysicalActivityQuestionnaire.pdf