The association between serum selenium with circulating levels of adipokine in patients with polycystic ovary syndrome

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Research Article

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Abstract

Growing evidence has shown a possible correlation between selenium (Se) and its main transport protein, selenoprotein-P (SePP), with polycystic ovary syndrome (PCOS). The Se and SePP link with adipokine levels in this group of individuals received insufficient attention, though. In the present study, we aimed to investigate the associations of Se and SePP with adipokine levels in patients with PCOS. In this cross-sectional study, 115 patients with PCOS aged 18–45 years, diagnosed based on Rotterdam Consensus criteria, were recruited. Participants’ general characteristics were collected using a general questionnaire and anthropometric measurements were taken. The blood sample was obtained, and serum levels of leptin, adiponectin, visfatin, resistin, and omentin-1, as well as glucose metabolism markers, were measured. Serum levels of Se and SePP were inversely correlated with fasting Blood Sugar (FBS), serum insulin, and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). In addition, serum levels of Se and SePP positively correlated with adiponectin and visfatin serum levels. Although there was no significant correlation between serum Se and serum omentin-1 levels, a significant positive correlation was found between the serum levels of SePP and this adipokine. The present study found that serum Se and SePP levels were positively correlated with serum adiponectin and visfatin levels. Further studies are required to confirm these findings.

Introduction

Polycystic ovary syndrome (PCOS) is among the most prevalent endocrine disorders affecting 5–20% of women in their fertility years worldwide [1, 2]. PCOS is likely the result of genetic and environmental factors [3] and is characterized by hyperandrogenism, oligoanovulation, and polycystic ovaries [4]. PCOS is associated with various manifestations such as oligomenorrhea and amenorrhea, hirsutism, alopecia, acne, infertility, obesity, insulin resistance (IR), and chronic inflammation [5, 6]. Moreover, this condition imposes huge financial burdens on those affected by it and the health care system as well [7].

Excessive adipose tissue in PCOS women leads to chronic inflammation by releasing pro-inflammatory cytokines [8]. Also, extra adipose mass alters the secretion of adipokines [9]. Leptin, an adipokine regulating energy balance, is increased in patients with PCOS [10, 11], which prevents the conversion of androgens to estrogen by inhibiting the expression of aromatase mRNA in granulosa cells [12]. Adiponectin is an anti-inflammatory adipokine with insulin-sensitizer properties that has a pivotal role in the elevation of ovulation and the production of estrogen and progesterone [12, 13]. Women with PCOS are reported to have lower circulating adiponectin levels [14]. Another adipokine with decreased serum level in PCOS is omentin-1 [8]. Low levels of omentin-1, independent of body mass index (BMI), are associated with IR [15]. Most studies have reported elevated levels of resistin mRNA and visfatin in PCOS, which are linked to IR, high androgen serum concentrations, and cyst formation [16–18].

Selenium (Se) is a micronutrient mostly known for its antioxidant activities [19]. However, it is also involved in several other functions, including endocrine and metabolic activities. Se deficiency is associated with several chronic disorders such as cardiovascular diseases, cancer, and death [20]. This
essential nutrient mainly applies its specific functions through selenoproteins. For example, downregulation of selenoprotein-P (SePP) expression has been found to improve systemic insulin sensitivity and glucose tolerance [21]. It is believed that Se status might be affected by the inflammatory condition of PCOS [22]. Low plasma concentrations of Se in women with PCOS result in hyperandrogenism [23]. Improvement of endocrine and metabolic features and ovarian functions in PCOS depends on sufficient levels of Se [24]. Several randomized clinical trials assessed the effect of Se supplementation on PCOS; the finding of a systematic review and meta-analysis summarizing these studies indicated that supplementation of selenium did not improve the level of glycemic indices including Homeostatic Model Assessment for Insulin Resistance index (HOMA-IR) and fasting Blood Sugar (FBS) [7]. Limited observational studies examined Se levels in PCOS women [25, 26] or relationships between Se concentration and odds of PCOS [27]; however, we are unaware of any study examining the link between Se and SePP with adipokines. Therefore, this study aimed to assess the association of serum Se and SePP with serum levels of adipokines, including leptin, adiponectin, omentin-1, resistin, and visfatin in patients with PCOS.

Materials and methods

Patients

This cross-sectional study was conducted on 115 females diagnosed with PCOS aged 18–50 years who attended the Reproductive Health Centre affiliated with Zabol University of Medical Sciences from January to May 2023. The sample size was calculated based on data obtained from the study established by Misu et al. [28] for serum adiponectin as one of the study's main dependent variables. Considering $r=-0.3$, $\alpha = 0.05$, and a power of 90%, we attained a sample size of 115 subjects.

In this study, the diagnosis of PCOS among participants was based on criteria stipulated by the Rotterdam Consensus [29]. Thus, participants were deemed to have PCOS if they had at least two of the three criteria: 1) having chronic amenorrhea or oligomenorrhea; 2) the presence of clinical and laboratory signs of hyperandrogenism; 3) having polycystic ovaries. The subjects were also excluded if taking antioxidant supplements like Se, carotenoids, and vitamins E and C, as well as any medications known to induce metabolic or hormonal changes such as estrogens, metformin, corticosteroid drugs, and lipid-lowering medications within three months before enrollment the study.

Biochemical analyses

After a 10-hour overnight fasting period, 10 ml of venous blood sample was taken from the antecubital vein in the morning. The blood sample was centrifuged (3,000 rpm for 10 min at 4°C for serum acquisition) and stored at −80°C until the analysis time.

Serum levels of FBS were measured via the enzymatic colorimetric method using an automatic analyzer (Abbott, model Alcyon 300, USA) by commercial kits (Pars-Azmoon Co., Tehran, Iran). Serum insulin levels were measured with an enzyme-linked immunosorbent assay (ELISA) kit (DiaMetra, Milano, Italy)
according to the manufacturer's instructions. Insulin resistance was assessed by calculating the HOMA-IR according to the suggested formula [30]. Serum levels of adiponectin, leptin, resistin, visfatin and omentin-1 were measured using ELISA kits (Bioassay Technology Laboratory, Shanghai Korean Biotech, Shanghai City, China). The intra- and inter-assay coefficients of variation (CVs) for all the biochemical assays were less than 6% and 9%, respectively.

Serum levels of Se were measured by a hydride generation atomic absorption spectrophotometer (Atomic absorption spectrophotometer Shimadzu, AA-680, Japan) using a pyrolytically coated graphite furnace (GFA-EX7i), a selenium hollow cathode lamp operated with a 196.0 nm wavelength, 23 mA current, 0.7 nm bandpass, and deuterium background corrector. Serum levels of SePP were measured using human ELISA kit (USCN Life Science, Wuhan, China) according to the manufacturer's instructions.

Assessment of other variables

All the participants completed a general questionnaire and underwent anthropometric measurements. Height was measured using a wall stadiometer. A digital scale was applied to measure the weight of the participants in a standing position while they wore light clothing without shoes. BMI was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured twice using a flexible non-elastic tape at the midpoint between the iliac crest edge and the bottommost rib at the end of a normal exhalation [31]. Obesity was considered as BMI $\geq 30$ kg/m² [32].

Statistical analysis

All Statistical analyses were performed using the Statistical Package for the Social Sciences software version 25 (IBM Corp., Armonk, NY, USA). In all the analyses, a $p$-value of less than 0.05 was considered statistically significant. Kolmogorov–Smirnov test was applied to evaluate the normal distribution of the variables. Continuous variables are displayed as Mean ± standard deviation (SD), while the qualitative variables were reported as percentages and frequency. One-way analysis of variance (ANOVA) and Pearson chi-square tests was used to explore the differences between quantitative and categorical variables across the tertiles of Se and SePP, respectively. Pearson correlation coefficients were applied to examine the relationship between serum levels and Se and SePP with serum levels of adipokines and glucose metabolism markers.

Results

The study samples comprised 115 females with PCOS whose mean age and BMI were 33.7 ± 6.1 years and 28.0 ± 3.0 kg/m², respectively. The mean serum levels of Se and SePP in the samples were 59.1 ± 9.2 µg/l and 4.1 ± 1.1 µg/ml, respectively. Demographic characteristics and glucose metabolism markers in the participants are illustrated in Table 1. The mean age, weight, BMI, and WC were identical across tertiles of serum Se and SePP levels. In addition, there was no significant difference in the proportion of subjects with obesity across tertiles of serum Se and SePP levels. The mean serum levels of insulin and HOMA-IR had a diminishing trend across the elevation of serum Se and SePP tertiles ($P<0.05$ for all).
Nonetheless, no significant differences were found regarding FBS across tertile categories of serum Se and SePP levels.

### Table 1
Demographic characteristics and glucose metabolism markers in the patients with PCOS across tertiles of serum selenium and selenoprotein P levels

<table>
<thead>
<tr>
<th>Variables</th>
<th>Serum selenium tertiles</th>
<th></th>
<th></th>
<th>Serum selenoprotein P tertiles</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1 (n = 38)</td>
<td>T2 (n = 39)</td>
<td>T3 (n = 38)</td>
<td>T1 (n = 39)</td>
<td>T2 (n = 38)</td>
<td>T3 (n = 38)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.5 ± 5.4</td>
<td>34.4 ± 6.3</td>
<td>33.2 ± 6.8</td>
<td>0.659</td>
<td>34.2 ± 5.5</td>
<td>34.7 ± 5.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.7 ± 9.6</td>
<td>72.4 ± 6.5</td>
<td>71.6 ± 9.3</td>
<td>0.262</td>
<td>74.5 ± 6.9</td>
<td>73.2 ± 9.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.4 ± 6.7</td>
<td>161.9 ± 7.5</td>
<td>159.5 ± 5.6</td>
<td>0.129</td>
<td>162.1 ± 6.3</td>
<td>161.7 ± 7.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.3 ± 3.2</td>
<td>27.7 ± 2.9</td>
<td>28.1 ± 3.0</td>
<td>0.688</td>
<td>28.4 ± 2.3</td>
<td>28.0 ± 3.4</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>93.5 ± 9.8</td>
<td>91.0 ± 9.1</td>
<td>94.1 ± 9.7</td>
<td>0.321</td>
<td>91.8 ± 8.7</td>
<td>94.7 ± 11.2</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>11 (28.9)</td>
<td>10 (25.6)</td>
<td>15 (39.5)</td>
<td>0.395</td>
<td>11 (28.2)</td>
<td>12 (31.6)</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>106.0 ± 14.8</td>
<td>104.2 ± 10.5</td>
<td>101.7 ± 9.6</td>
<td>0.119</td>
<td>106.7 ± 16.8</td>
<td>103.5 ± 9.9</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>20.0 ± 7.2</td>
<td>17.4 ± 5.7</td>
<td>16.5 ± 4.6</td>
<td>0.013</td>
<td>19.6 ± 7.4</td>
<td>17.5 ± 5.4</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>5.3 ± 2.5</td>
<td>4.6 ± 2.0</td>
<td>4.2 ± 1.3</td>
<td>0.015</td>
<td>5.3 ± 2.9</td>
<td>4.9 ± 1.5</td>
</tr>
</tbody>
</table>

PCOS, polycystic ovary syndrome; BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose; HOMA-IR, homeostasis model of risk assessment-insulin resistance

*a* Data are illustrated as mean ± standard deviation unless indicated otherwise.

*b* Tertile cut-points of serum Se concentrations are as follows: first, < 55.24; second, 54.24 to 63.23; third, > 63.23

*c* Tertile cut-points of serum selenoprotein P concentrations are as follows: first, < 3.57; second, 3.57 to 4.51; third, > 4.51

*d* Obtained from one-way ANOVA test or Pearson chi-square test for continuous or categorical variables, respectively
Table 2 illustrates the mean serum of adipokines in the patients with PCOS by tertiles of serum Se and SePP levels. The mean serum levels of adiponectin had decreasing trends across the increase of serum Se (P-trend = 0.009) and SePP (P-trend < 0.001) tertiles. Likewise, there was a trend towards increasing serum visfatin levels with the enhancement of tertile categories of both serum Se (P-trend = 0.016) and SePP (P-trend = 0.002) levels. The mean serum levels of omentin-1 had regularly increasing trends across the enhancement of serum SePP levels (P = 0.002). Nonetheless, serum levels of Se were not associated with serum omentin-1 levels. Moreover, no significant regular trend was observed regarding serum leptin and resistin across serum Se and SePP levels (Table 2).

Table 2
Serum levels of adipokines in the patients with PCOS across tertiles of serum selenium and selenoprotein P levelsa

<table>
<thead>
<tr>
<th>Variables</th>
<th>Serum selenium tertilesb</th>
<th>Serum selenoprotein P tertiles c</th>
<th>P-trendd</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1 (n = 38)</td>
<td>T2 (n = 39)</td>
<td>T3 (n = 38)</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>28.5 ± 15.9</td>
<td>33.3 ± 17.6</td>
<td>32.3 ± 17.9</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>15.5 ± 6.6</td>
<td>17.7 ± 8.9</td>
<td>20.5 ± 8.7</td>
</tr>
<tr>
<td>Visfatin (ng/mL)</td>
<td>13.1 ± 4.0</td>
<td>15.8 ± 7.7</td>
<td>17.3 ± 9.8</td>
</tr>
<tr>
<td>Resistin (ng/mL)</td>
<td>5.8 ± 0.9</td>
<td>6.2 ± 1.1</td>
<td>6.1 ± 1.1</td>
</tr>
<tr>
<td>Omentin-1 (ng/mL)</td>
<td>213.5 ± 65.8</td>
<td>218.4 ± 66.9</td>
<td>217.8 ± 78.3</td>
</tr>
</tbody>
</table>

PCOS, polycystic ovary syndrome

aData are illustrated as mean ± standard deviation.

bTertile cut-points of serum Se concentrations are as follows: first, < 55.24; second, 54.24 to 63.23; third, > 63.23

cTertile cut-points of serum selenoprotein P concentrations are as follows: first, < 3.57; second, 3.57 to 4.51; third, > 4.51

dObtained from one-way ANOVA test

The correlation coefficients of serum Se and SePP with glucose metabolism markers and serum levels of adipokines are illustrated in Table 3. Serum levels of Se and SePP were inversely correlated with FBS, serum insulin, and HOMA-IR. In addition, serum levels of Se and SePP positively correlated with serum levels of adiponectin and visfatin. Although there was no significant correlation between serum Se and
serum omentin-1, a significant positive correlation was observed between the serum levels of SePP and serum levels of this adipokine (Table 3).

Table 3  
Pearson's correlation coefficients between serum selenium and selenoprotein P levels with adipokines in the patients with PCOS (n = 115)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Serum selenium levels</th>
<th>Serum selenoprotein P levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>-0.198</td>
<td>0.034</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>-0.262</td>
<td>0.005</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-0.272</td>
<td>0.003</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>0.101</td>
<td>0.283</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>0.274</td>
<td>0.003</td>
</tr>
<tr>
<td>Visfatin (ng/mL)</td>
<td>0.328</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Resistin (ng/mL)</td>
<td>0.121</td>
<td>0.196</td>
</tr>
<tr>
<td>Omentin-1(ng/mL)</td>
<td>0.119</td>
<td>0.206</td>
</tr>
</tbody>
</table>

PCOS, polycystic ovary syndrome; FBG, fasting blood glucose; HOMA-IR, homeostasis model of risk assessment-insulin resistance

Discussion

Our observations indicated a positive correlation between serum levels of Se and SePP with adiponectin and visfatin. Se serum levels were not significantly correlated with omentin-1, although; we found a significant positive link between the serum levels of SePP and this adipokine. Based on our knowledge, this is the first study to investigate the association between serum Se and SePP with adipokines levels in PCOS patients.

PCOS is a prevalent metabolic and endocrine syndrome among women [33]. Considering the high oxidative stress and the inflammatory state of PCOS, it has been speculated that Se and SePP, anti-inflammatory and anti-oxidant agents, to be associated with PCOS and its complications [24, 34, 35]. In the present survey, we investigated the association between serum levels of Se and SePP with glucose metabolism agents, as it is assumed that PCOS metabolic abnormalities are primarily linked to IR [36]. And observed that FBS, serum insulin, and HOMA-IR decreased with increasing Se and SePP serum levels. However, some studies seem to disagree with the aforementioned findings. Namely, a case-control study reported no significant association between SePP with FBS, serum insulin, and HOMA-IR in patients with PCOS [34]. Moreover, in a randomized control trial (RCT) study, PCOS women who received daily selenium supplement for 8 weeks benefited from their inverse effects on insulin and HOMA-IR; however,
Se supplementation did not change FBS levels [37]. Inversely, Se supplementation led to a marginal increase in insulin levels without any significant change in FBS [38]. A systematic review and meta-analysis summarizing the findings of five RCTs that stated compared to the control group, Se supplementation was associated with significantly reduced FBS and HOMA-IR in PCOS patients [39]. Findings from large-scale observational cohort studies are required to illuminate these conflicting results. Although the exact mechanisms through which Se and SePP participate in improving of IR remain to be elucidated, several mechanisms have been proposed. Se may improve insulin resistance by regulating of cellular insulin signaling in hepatocytes and myocytes by inactivating adenosine monophosphate-activated protein kinase (AMPK) [40]. Another possible mechanism in which SePP and insulin resistance correlation could be explained is that SePP and gluconeogenic enzyme expression seems to be linked, leading to the promotion of de novo biosynthesis of glucose [41]. Moreover, we examined the link between Se and SePP with adipokine levels as a possible underlying mechanism in PCOS pathogenesis, as well. Serum levels of Se and SePP were positively correlated with circulating levels of adiponectin and visfatin, in this study. Although there was no significant correlation between serum Se and omentin-1, a significant positive correlation was observed between SePP and serum levels of this adipokine. The available data regarding the relationship between Se and SePP with adipokines in patients with PCOS are limited. Nevertheless, Misu et al. [28] found that serum SePP levels were negatively associated with adiponectin circulating levels in diabetic patients. In a double-blind, placebo-controlled trial on five hundred and one individuals who were randomly allocated to selenium or placebo-receiving groups, Se supplementation was not found to be effective on adiponectin levels after six months of treatment. However, they observed an inverse association between plasma Se and adiponectin concentrations at baseline of their investigation [42]. Even though that there is still much to discover about involved cellular mechanisms, animal models have shown that adiponectin gene expression tended to be increased in the gene encoding SePP-1 knockout mice [28]. Interestingly, the knockdown of this gene also improved glucose intolerance and insulin resistance in mice [43].

To the best of our knowledge, the present study was the first to examine the association between serum Se and SePP with circulating adipokines in patients with PCOS. It is noted also that the panel of biomarkers used in this study was fairly comprehensive regarding adipokines that could be expected to be dysregulated in Se deficiency. However, the current study had some limitations that should be considered. These results could be biased by unrecognized confounders, as with all observational studies. Causality evaluating is not possible due to the cross-sectional design of the study.

Conclusion

In conclusion, the present study provides evidence suggesting that serum Se and SePP is positively associated with serum adiponectin and visfatin levels. In addition, serum SePP was associated with serum omentin-1 levels. No significant relationship was observed between serum Se and omentin-1. Prospective observational studies are needed to examine such relations comprehensively.
Declarations

Author contributions: Zeinab Khademi: Project administration, Visualization, Writing original draft. Sanaz Pourreza: Writing – original draft. Soudabeh Hamedi-Shahraki: Methodology, Software, Formal analysis, Validation. Farshad Amirkhizi: Conceptualization, Supervision, Data curation, Writing – review & editing.

Funding: The financial support for this study comes from Zabol University of Medical Sciences.

Data availability: The dataset supporting the conclusions of this article is available from the corresponding author.

Statements and Declarations

Conflict of interest: The authors declare that they have no competing interests.

Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Zabol University of Medical Sciences (ethics code number: IR.ZBMU.REC.1401.103).

Informed consent: Before data collection, the objectives and protocol of the research were explained to participants before signing written informed consent.

Acknowledgements

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References


