Journal of Nutrition and Food Security
Shahid Sadoughi University of Medical Sciences
School of Public Health
Department of Nutrition
Nutrition & Food Security Research Center

eISSN: 2476-7425 pISSN: 2476-7417 JNFS 2024; 9(1): 52-58 Website: jnfs.ssu.ac.ir

Selenium Concentrations in Patients with Depression: A Case-Control Study

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ARTICLE INFO

ORIGINAL ARTICLE

Article history:
Received: 13 Apr 2022
Revised: 28 May 2022
Accepted: 6 Jul 2022

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ABSTRACT

Background: Evidence suggests that dietary micronutrients may be associated with depression. The role of selenium as a risk or protective factor for depression was contradictory. Therefore, this study aimed to investigate the association between serum selenium concentrations and depression. **Methods:** This case-control study was conducted from 2018 to 2020 in Shahrekord, Iran. The case and control groups included patients with or without depression, respectively. Seventy-two participants were selected using the conventional method. In addition to recording demographic variables, the blood selenium concentration of the participants was measured. **Results:** There was no difference between case and control groups in terms of mean levels of blood selenium (P>0.05). Results showed that there was no statistically significant interaction between the effects of gender and group (P=0.51), age and group (P=0.13), Body mass index (BMI) and group (P=0.52) on blood selenium concentrations. However, females had significantly more selenium concentrations than males in both groups (P=0.005). **Conclusion:** Despite some confirming evidence for the association of depression and blood selenium concentration, this study did not show such a relationship. However, blood selenium concentration was higher in women than men in both groups.

Keywords: *Selenium; Depression; Patients; Iran; Case-control studies*

Introduction

Depression is the most prevalent psychiatric disorder and a major global health problem (Mahmoud *et al.*, 2020). The current view of the cause of depression is a prototype model of gene-environmental interaction (Krapohl *et al.*, 2017, Nemeroff, 2008). Among the environmental factors, micronutrients can be mentioned. Epidemiological evidence in adults has shown an association between depression and micronutrient deficiencies, including B vitamins (Almeida *et al.*, 2015), vitamin E (Farhadnejad *et al.*, 2020), and vitamin D (Anglin *et al.*, 2013). Laboratory

This paper should be cited as: Zarean E, Sadeghi P, Jafari T, Malekpour Tehrani A, Torkian S. ***Selenium Concentrations in Patients with Depression: A Case-Control Study.*** *Journal of Nutrition and Food Security (JNFS)*, 2024; 9 (1): 52-58.

[DOI: 10.18502/jnfs.v9i1.14840]

evidence also suggests some or all of depression symptoms reduced by improving micronutrient deficiencies (Campisi *et al.*, 2020).

Selenium is one of the essential micronutrients for humans. Although, in large doses, it can be toxic and cause side effects (Wang *et al.*, 2017). Selenium can reduce inflammation by modulating the expression of selenoprotein genes (Pasco *et al.*, 2012). For this reason, it has been suggested that selenium may play a role in inflammatory diseases, including depression (Pasco *et al.*, 2012). Selenium has significant modulatory effects on dopamine. Dopamine is involved in the pathophysiology of depression and other psychiatric disorders (Torres, 2017). In addition, selenium is essential for the proper synthesis of thyroid hormones. Changes in these hormones are associated with neuropsychiatric manifestations such as mood disorders, cognitive dysfunction, and other psychiatric symptoms (Młyniec *et al.*, 2015). But the evidence is limited and contradictory (Wang *et al.*, 2018).

A cross-sectional study on farmers in southeastern Brazil reported that high doses of selenium were associated with a reduction of about 54% in the chance of depression after adjusting for sociodemographic variables, lifestyle, and pesticide intoxication (de Almeida *et al.*, 2021). In another study in New Zealand, the prevalence of minor depression was higher in the second-class plasma selenium tertiles (Jin *et al.*, 2020). Polish-Norwegian Study (PONS) cohort showed that depression was affected by low selenium intake, blood selenium concentration, and depression (Ghimire, 2017). A study on adults aged 18 years or older reported that total selenium intake was inversely associated with depression. Participants who met recommended dietary selenium allowance had lower odds of depression (Li *et al.*, 2018). Due to limited evidence, a review article reported inconclusive results about the relationship between depression and selenium (Wang *et al.*, 2018). Similarly, a meta-analysis emphasized the small number of studies in this field (Sajjadi *et al.*, 2022).

This is the first study conducted in Iran regarding the relationship between selenium and depression. According to meta-analyses published in 2022, there are less than 10 articles in this regard, and there is still controversy. One of the present study innovations was using blood samples to check selenium. Therefore, this study was conducted to investigate the association between selenium concentrations and depression. The study results can be helpful to clarify this relationship. These results may contradict or agree with previous studies.

Materials and Method

Study design: This case-control study was conducted from 2018 to 2020 in Shahrekord, Iran. The participants were patients referred to cardiac, internal medicine, and psychiatric clinics affiliated with Shahrekord University of Medical Sciences. Inclusion criteria included age of 18 to 60 years, no chronic and debilitating disease, no multivitamin use in the last six months, and no smoking. The exclusion criteria were diabetes mellitus, hypothyroidism, any gastrointestinal disorder, uncontrolled hypertension, any kinds of cancer, alcohol abuse or dependency, renal disease, and illiteracy. In fact, the restriction method was used in the design phase to control potential confounders. The case group included patients with depression. The control group was patients who had been referred to the mentioned clinics for a check-up and had no depression. Samples were selected by convenience sampling method. Beck Depression Inventory (BDI) and psychiatrist's approval were used to diagnose depressed and non-depressed people.

Sample size: With consideration of effect size 0.6 (between medium (0.5) and large (0.8) effect size) (Lakens, 2013), power 80%, confidence level 95%, and allocation ratio N2/N1=1, the total sample size was calculated as 72 people (36 people in each group) via G*Power version 3.1.9.4. Finally, 33 cases and 39 controls were enrolled in the study.

Measurements: The variables studied in this study included demographic variables, depression, and blood selenium levels (mg/l). Demographic

[DOI: 10.18502/jnfs.v9i1.14840]

variables included gender (female/male), age (year), and body mass index (BMI) including underweight (Below 18.5), normal (18.5–24.9), overweight (25.0–29.9), and obese (30.0 and Above) categories (CDC, 2020). Depression was measured by BDI. Blood samples were used to determine selenium concentrations (mg/l).

BDI was used to assess depression symptoms. This questionnaire consisted of 21 questions with a 4-point Likert (0-3). The minimum score of this questionnaire was zero, and the maximum was 63. A score of less and equal to 13 indicated no depression (control group), a score of more than 13 demonstrated depression (case group) (Kim *et al.*, 2019).

Intravenous blood sampling was performed with a volume of 5 ml. Blood samples in CBC tubes containing EDTA were delivered to the laboratory within a maximum of 48 hours and stored at refrigerator temperature (4°C). A variant 220 atomic absorption spectrophotometer was used to measure selenium, which was equipped with a graphite furnace with a background correction system (model of Zeiman Z110). Regarding tothe method described by Zanao (Zanao *et al.*, 2002), sample preparation was performed by mixing 200 µl of the sample with 800 µl of 2% nitric acid solution and Triton X-100 (0.5%, volume to volume). Finally, 20 microliters of the resulting solution with ten microliters of modifier solution (including palladium 0.05% weight by volume) and magnesium nitrate 0.03% weight by volume) was injected into the device. Selenium concentration was measured at 196 nm and width 0.7 nm. The thermal program of the device included drying the first stage at 110 °C, drying the second stage at 130 °C, ash at 1100 °C, atomizing at 1900 °C, and the clearance at 2450 °C. Calibration curve at concentrations of 5 to 50 µg per liter was used to determine selenium concentration of samples. The reference range for plasma selenium was about 60–150 ng/ml (Smith and Garg, 2017). Selenium deficiency was serum concentration <40 ng/ml, and toxic levels have not yet been well defined (Smith and Garg, 2017).

Data analysis: In the descriptive analysis, mean ± standard deviation (SD), frequency (n), percent (%), median, and interquartile range (IQR) were used. Chi-square, Exact, Mann-Whitney, T-test, and two-way ANOVA tests were used for analytical analysis. Chi-square and Exact tests were utilized for assessing dependency on gender and BMI with study groups (case and control). Mann-Whitney test was utilized for evaluating the difference between study groups according to age. T-test was used to assess the difference between the blood selenium mean of case and control groups. The selenium mean differences between groups concerning two independent variables (age and group, gender and group, BMI and group) were examined by two-way ANOVA test. The normality of data and homogeneity of variances were respectively evaluated by Shapiro-Wilk test and Levene's test. All statistical analyses were performed in SPSS software. A p-value of less than 0.05 was considered statistically significant.

Ethical considerations: The proposal of this study was approved by Shahrekord University of Medical science viva ethics code IR.SKUMS.REC.1398.022. All participants signed and approved the informed consent form.

Results

The mean±SD age of the participants was 24.15±9.76 years. The majority of participants were female (72.2%) and with normal BMI (44.4%). There was no difference between case and control groups in terms of age, sex, and BMI (P>0.05, **Table 1**).

The assumptions of doing two-way ANOVA test were checked. The dependent variable (blood selenium concentrations (mg/l)) was measured at the continuous level. The two independent variables (age and group, gender and group, BMI and group) consisted of two or more categorical, independent groups. There was no relationship between the observations in each group and the groups themselves. Blood selenium concentrations had approximately normal distribution for each combination of the cells of the age and group, gender and group, and BMI and group variables

[DOI: 10.18502/jnfs.v9i1.14840]

(*P*>0.05). There was homogeneity of variance for the same cells (*P*>0.05).

Results of two-way ANOVA showed that there was no statistically significant interaction between the effects of gender and group level (case and control) (df=1, mean square=63.74, F=0.42, *P*= 0.51), age and group level (df=1, mean square=363.98, F=2.26, *P*=0.13), and BMI and group level (df=3, mean square=109.69, F=0.64, *P*=0.52) on selenium concentrations (**Table 2**). The main effects analysis showed that females had significantly more blood selenium concentrations than males in both case and control groups (*P*=0.005). There was no difference main effects for age and BMI (*P*>0.05, **Table 2**).

Figure 1 shows blood selenium concentrations in case and control groups compared to all people.

Table 1. The characteristics of the participants (n=76: case=33, control=39)

Variables	Total	Case	Control	P-value
Age (y)	24.15 ± 9.76[a]	35.60 ± 10.62	32.92 ± 8.92	0.23[d]
(Median (IQR))	33.50 (14.75)[b]	35.00 (15.00)	31.00 (14.00)	
Gender				
Male	20 (27.8)[c]	7 (21.2)	13 (33.3)	0.25[e]
Female	52 (72.2)	26 (78.8)	26 (66.7)	
Body mass index				
Underweight	2 (2.8)	0 (0)	2 (5.1)	0.06[f]
Normal	32 (44.4)	11 (33.3)	21 (53.8)	
Overweight	30 (41.7)	16 (48.5)	14 (35.9)	
Obese	8 (11.1)	6 (18.2)	2 (5.1)	

[a]: Mean±SD; [b]: median (IQR); [c]: N(%); [d]: Mann-Whitney Sig. (2-side); [e]: Chi-square Sig. (2-sided); [f]: Exact Sig. (2-sided).

Table 2. Compere of blood Selenium concentrations (mg/l) in Case (depression) and Control (health people) groups according independent variables (case=33, control=39).

Variables	Total	Case	Control	P-value [a]	P-value[b]	P-value[c]
Overall	103.73 ± 12.65	103.72 ± 10.58	103.75 ± 14.31	-	-	0.99
Age (y)						
<35	104.60 ± 12.87	102.51 ± 13.04	106.11 ± 12.80	0.137	0.52	0.74
>35	102.44 ± 12.43	105.16 ± 6.73	99.53 ± 16.32			
Gender						
Male	97.30 ± 16.71	94.47 ± 11.38	98.82 ± 19.24	0.516	0.005	0.51
Female	106.21 ± 9.82	106.20 ± 9.05	106.21 ± 10.72			
Weight status						
Underweight	101.43 ± 9.77	-	101.43 ± 9.77	0.526	0.64	0.46
Normal	102.43 ± 14.27	100.41 ± 13.54	103.49 ± 14.85			
Overweight	104.46 ± 12.23	105.66 ± 9.11	103.08 ± 15.29			
Obese	106.80 ± 8.19	104.58 ± 7.99	113.45 ± 5.72			

[a] Two-way ANOVA, interaction between independent variable and group; [b] Two-way ANOVA, main effect of independent variables; [c] Two-way ANOVA, main effect of group

[DOI: 10.18502/jnfs.v9i1.14840]

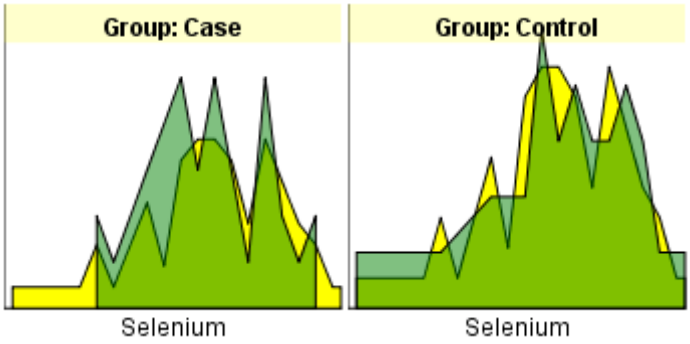

Figure 1. Blood selenium concentrations in case and control groups compared to all people (Yellow: all people, Green: case or control group)

Discussion

This study showed no difference in blood selenium concentration between the case and control groups, but blood selenium concentration was higher in women in both groups.

In line with the present study, a nested case-control study in 2012 was conducted on women aged 20 years or more and showed an inverse association between selenium intake and major depressive disorder. However, this association was not significant (Pasco *et al.*, 2012). Another cross-sectional study in 2019 presented that serum selenium concentrations were not associated with depressive symptoms (Ghimire, 2017). Similar to the current study, a cross-sectional research on hemodialysis patients aged 18 to 85 years in Shiraz, Iran, demonstrated no significant difference in serum selenium levels between depressed hemodialysis patients and the rest of the patients without depression (Ekramzadeh *et al.*, 2015). In 2021, a cross-sectional study conducted on female students in Zahedan, Iran, showed no significant association between selenium intake and depression score (Shokati *et al.*, 2021). In 2022, a systematic review and meta-analysis showed no significant differences in serum selenium levels between depressed patients and healthy subjects. They also reported no significant correlation between serum levels of selenium and depression scores (Sajjadi *et al.*, 2022). These results approve the present study results.

Contrary to the present study, a cross-sectional study in the United States showed an inverse association between total selenium intake and depression (Li *et al.*, 2018). A cohort study in 2014 on 20-32-year old participants of US reported that doubling of the selenium level was associated with 56% higher odds of having depressive symptoms (Colangelo *et al.*, 2014). A meta-analysis with six observational studies concerning dietary selenium intake showed that dietary selenium intake was negatively associated with depression (Ding and Zhang, 2022). A cohort study in south-eastern Australia showed that low selenium intakes increased the likelihood of developing the major depressive disorder after a decade of follow-up (Pasco *et al.*, 2012).

Demographic variables and health status may affect serum selenium concentrations (Sajjadi *et al.*, 2022). Most of the confounding variables were ignored in previous studies (Sajjadi *et al.*, 2022). In the present study, many potential confounder factors were adjusted.

Differences between study results can be due to the type of study (cross-sectional, case-control, cohort, or interventional study), depression measurement method (types of available questionnaires), different questionnaires cut-off for depression, selenium measurement methods (such as blood or nails sample, or questionnaire tools), and adjusting confounding factors.

The current study has several strengths. Selenium levels were measured using blood samples. The study included participants who had not taken dietary supplements. Hence the ascertained selenium levels can be measured

[DOI: 10.18502/jnfs.v9i1.14840]

without the effect of supplements. This study adjusted many potentially confounding variables that could distort the results by reviewing extensive literature. Taking a control group from medical centers modulated unknown confounding variables.

One of the limitations of this study was that the case group did not reach 36 people despite a two-year employment period. Moreover, due to the restriction method, the effect of potential confounders on the association between selenium and depression could not be measured, like their interaction forms. The small sample size in this study could be another limitation. It is recommended to use smaller size effects in future studies.

Conclusion

Despite some confirming evidence for the association of depression and blood selenium concentration, this study did not show such a relationship. Further investigations are required to reach a clear conclusion. Other studies focusing on different methods of measuring selenium in depressed individuals and control groups are recommended.

Acknowledgment

Thanks are owed to Shahrekord University of Medical Sciences for financially supporting the project and all participants for their cooperation in the study.

Authors' contributions

Zarean E, Jafari T, and Malekpour Tehrani A in writing the proposal; Zarean E, Jafari T, Malekpour Tehrani A, and Sadeghi P in collecting samples; Torkian S, Sadeghi P, and Zarean E in sorting and analyzing the data; Torkian S, Zarean E, and Sadeghi P in writing the initial draft; and Torkian S, Zarean E, Jafari T, Malekpour Tehrani A, and Sadeghi P in finalizing the final draft. All authors have read and approved the final draft.

Conflict of interests

The authors declare no conflict of interest.

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[DOI: 10.18502/jnfs.v9i1.14840]