Original Article

Effect of Selenium Supplementation on Lipid Profile, Anemia, and Inflammation Indices in Hemodialysis Patients

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ABSTRACT

Objective: Trace elements deficiency is common among end-stage renal disease (ESRD) patients due to excessive loss during dialysis and the lower intake secondary to loss of appetite. Selenium (Se) is a trace element that plays an important role in the radical scavenging system and helps the body defend against oxidative stress. This study aims to evaluate the effects of Se supplementation on lipid profile, anemia, and inflammation indices in ESRD patients. **Methods:** Fifty-nine hemodialysis patients enrolled and were randomly divided into two groups. Two hundred microgram Se capsules once daily for the case group and matching placebo for the control group were administered for three months. Demographic data were collected at the study beginning. Uric acid (UA), anemia and inflammation indices, and lipid profiles were recorded at the beginning and the end of the study. **Findings:** UA and UA-to-HDL (high-density lipoprotein) ratio decreased significantly in the case group ($P < 0.001$). The changes in lipid profile were not significant among both groups. Hemoglobin slightly increased in the case group, however, it decreased significantly in the control group ($P = 0.031$). High-sensitivity C-reactive protein (hs-CRP) decreased in the case group and increased in the control group, however, none of these changes were significant. **Conclusion:** According to the results of this study, selenium supplementation in ESRD patients could reduce some risk factors related to their mortality, such as the ratio of uric acid to HDL. However, the changes related to lipid profile, hemoglobin level and hs-CRP biomarker were not significant.

KEYWORDS: *Anemia, hemodialysis, inflammation indices, lipid profile, Selenium*

INTRODUCTION

Chronic kidney disease (CKD) is a general term for some diseases which affect kidneys; however, this term is used for a condition, in which kidneys are damaged permanently and irreversibly. Furthermore, CKD is progressive and gets worse as time passed. End-stage renal disease (ESRD) is the terminal stage of CKD, in which the glomerular filtration rate (GFR) falls to less than 15 mL/min. The most common cause of ESRD in the United States is diabetic nephropathy, while hypertension is recorded as the second. Cardiovascular disease (CVD) is the most common cause of death among ESRD patients.[1,2]

Besides CVD, complications such as inflammation and increased C-reactive protein (CRP), hypertension (HTN), bone and mineral disorders, hyperuricemia, metabolic acidosis, hyperphosphatemia, hypoalbuminemia, anemia, and peripheral vascular disease can be named for other side effects of ESRD.[3,4]

An alternative method of therapy for ESRD is dialysis (hemodialysis or peritoneal dialysis). In ESRD patients, the amount of trace elements and nutrient supply are reduced due to the loss of appetite, and losing these components through the dialysis process. This leads ESRD patients to a state of trace element deficiency. Among hemodialysis patients, about 90% were out of range regarding their body supplies of trace elements and nutrients.[4,5]

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Se is an element highlighted for its unique property as an antioxidant. Se is playing a role in thyroid hormone metabolism, the immune system, and the radical scavenging system.[6,7] Decreased mortality of CVD and regulation of inflammation mediators in asthma are other benefits of Se.[6]

It was shown that the serum level of Se in dialysis patients is lower than the average population which may pose a more complicated situation for this population. Furthermore, it is not clear whether Se supplementation in dialysis patients can compensate for this deficiency and overcome these complications.

This study was designed with the aim of investigating the effect of selenium administration in improving lipid profile, as well as indicators related to anemia and inflammation in patients undergoing hemodialysis.

Methods

The research project started at the beginning of 2019 and continued until the end of 2020. Patients were selected from the population referring to the dialysis clinics of Al-Zahra and Noor Hospitals, Isfahan, Iran. Sampling was done in a simple way, and every referring patient who met the inclusion criteria was included in the study if they signed the informed consent. The trial protocol was registered in the Iranian Registry of Clinical Trials (IRCT20160713028901N4), and approved by local ethics committee of Isfahan University of Medical Sciences with the following code: IR.MUI.MED.REC.1399.574.

Based on the before and after comparison of the variable with the highest variance, in a same previous study, changes in low-density lipoprotein cholesterol (LDL) were reported as 109.12 ± 31.12 and 85.66 ± 32.29, respectively,[8] and using the following formula, with the confidence interval of 95%, and the power of 80%, sample size achieved 35 per group. Finally, concerning probable excludes, 45 per group was considered as the sample size.

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times (\delta 1 + \delta 2)^2}{2 \times (\mu 2 - \mu 1)^2} = 35 \; per \; group$$

Individuals over 18 years of age who underwent hemodialysis for any reason were enrolled. Exclusion criteria included:

- Active hepatitis (based on several studies, in hepatitis B and C, Se levels will decrease)[9]
- Taking steroidal and nonsteroidal anti-inflammatory drugs at least 2 months before the study
- Taking any supplements containing Se at least 2 months before the study
- Lack of enough compliance for taking the product.

Patients' demographic and clinical characteristics, including age, sex, body weight, current illness, past medical history, duration of dialysis, and concomitant medications, were recorded.

After receiving written informed consent, the blocked randomization method was used to assign patients to intervention and control groups randomly. The recommended dietary allowance of Se for adult men and women 19+ years of age is 55 μg daily. The tolerable upper intake amount of Se for all adults 19+ years of age is 400 μg daily, which is the maximum daily dose unlikely to cause harmful effects on health.[10]

Due to our lack of knowledge about the basic level of Se in these patients, also to maintain the safety of patients and reduce the possibility of Se toxicity, and according to similar articles in this field, a Se supplement dose of 200 μg/day was chosen for the present study.[11]

In Zachara *et al.*'s study, three months of treatment with the same oral dose of Se was used to investigate the effect of Se in reducing DNA damage.[12]

For the intervention group, Se capsules at a dose of 200 μg per day, and for the control group, the placebo capsules were prescribed for three months. Both capsules were packed in similar containers and labeled concerning randomization codes. A physician evaluated the patient's clinical symptoms during the treatment period. Before and at the end of the study, high-sensitivity CRP (hs-CRP), lipid profiles including total cholesterol, triglyceride, LDL, and high-density lipoprotein (HDL) were measured.

In this study, to evaluate the compliance of patients, during routine visits, the remaining capsules were counted. If more than 20% of capsules have remained, the patient is excluded due to the lack of compliance.

All analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 16.0, IBM company, Chicago, Illinois, United States). To compare the basic demographic data between groups, an independent samples t-test was applied. Paired samples test was used to compare the parameter changes within each group. Furthermore, to compare the changes in parameters between the two groups, the analysis of covariance was used. $P < 0.05$ accounted for significance.

Results

Ninety-four patients who met the inclusion criteria and completed a written consent form were randomly allocated to one of two groups: intervention or control.

Of these, as demonstrated in the CONSORT diagram of the study [Figure 1], we excluded 35 patients (17 patients in the intervention group and 18 patients in the control group) due to unwillingness to continue the study, hospitalization, noncompliance and gastrointestinal adverse effects. As a result, 29 participants in the intervention group and 30 participants in the control group completed the study, and their data were finally analyzed. As shown in Table 1, the mean age of patients in the Selenium and the placebo groups was 54.37 ± 15.1 years and 54.06 ± 11.7, years, respectively. There were no significant differences between groups in Age, Weight, Height and BMI, at the beginning of study.

Table 2 shows the hematological parameters measured in two groups before and after the intervention. Uric acid, cholesterol, triglyceride, LDL, HDL, hemoglobin, serum iron, TIBC, transferrin, transferrin saturation, ferritin and hs-CRP were variables measured at the beginning and the end of intervention in both groups. At the study initiation, there was a significant difference between groups in lipid profile; so the ANCOVA test was used to compare the differences of these parameters at the end, to omit the basic differences.

Uric acid decreased significantly in the intervention group after three-months follow-up ($P < 0.001$). The changes in cholesterol, triglyceride, and LDL was not significant in both groups; however, HDL substantially increased in the intervention group ($P = 0.018$). While hemoglobin slightly increased in the intervention group, this parameter decreased significantly in the control group at the end of study ($P = 0.031$). Changes in other parameters were not significant.

Discussion

It is clear that inflammation plays a key role in many pathologic events in the body while oxidative stress is the most important reason. Regardless of ESRD patients' inflammation state, dialysis is a process that leads to inflammation independently. ESRD patients lose their nutrients during dialysis and also cannot compensate for it due to the loss of appetite. The body's radical scavenging system needs these nutrients and trace elements to defend against oxidative stress. Se is a trace element that plays a critical role in this system. It is shown that ESRD patients have Se deficiency. To evaluate whether Se supplementation can compensate the consequences of Se deficiency in ESRD patients, the related studies are discussed in following.

It is shown that Se supplementation can diminish selenium deficiency consequences. Atapour et al. showed that Se supplementation in ESRD patients increased serum level significantly; also, they found that patients' physical activity improved significantly after Se supplementation.[13]

There is a U-shaped association between serum UA level and CVD mortality, which can conclude that both hyperuricemia and hypouricemia are risk factors for CVD mortality. Some reports show this association between serum UA and the loss of kidney function. In our study, volunteers' serum UA levels were near to hyperuricemia range (>7.0 mg/dL for men and >6.0 mg/dL for women) at the beginning. Se supplementation could decrease the serum UA level of the case group significantly at the end compared to the beginning. The control group showed almost no change during the study. Some studies showed UA-lowering agents such as allopurinol or febuxostat, can slow renal disease progression in hyperuricemic subjects with mild-to-moderate CKD. However, it was not statistically significant, but these agents could increase the GFR. Finally, the administration of UA-lowering agents was associated with fewer CVD events. It is reported that allopurinol therapy reduces proteinuria in patients with diabetic nephropathy.[14]

In this study, in the beginning, the average triglyceride, LDL, and HDL for the control group were out of range; and their cholesterol was near borderline. For the case group, HDL was lower than the normal range at the start of the study. Some studies showed the association between low HDL and a high risk of CVD. The main roles of HDL in the body included anti-inflammation effect, vasoprotection, antiatherogenic properties, antiapoptotic effects, reversing the transport of cholesterol from peripheral tissues to the liver, preventing LDL oxidation, inhibition of platelet aggregation and stimulation of nitric oxide (NO) production. It is assumed that HDL lower than 40 for men and lower than 50 for women is a CVD risk factor. On the other hand, HDL in normal conditions can play its roles efficiently, but in

Table 1: Demographic information of the study population

Variable	Mean±SD		*P*
	Intervention group	Control group	
Age (years)	54.37±15.1	54.06±11.7	0.929
Weight (kg)	63.48±14.6	66.00±8.5	0.422
Height (cm)	165.03±8.8	165.4±8.6	0.873
BMI (kg/m^2)	23/2±4.4	24.1±2.4	0.304
Hemodialysis frequency (times/week)	3.03±0.4		
Hemodialysis duration (h)	3.98±0.2		
Kt/V	1.02 ± 0.45	0.95 ± 0.59	0.097

SD=Standard deviation, BMI=Body mass index, Kt/V is a measure of dialysis adequacy

Table 2: Mean values of the studied variables in intervention and placebo groups, before the initiation and after the end of the study

Variable	Mean±SD		*P*	Normal range
	Intervention group	Control group		
Uric acid (mg/dL)				
Before	6.48±1.12	5.93±1.14	0.064	3.6-8.1
After	5.62±1.08	5.93±1.08	0.33	
P	0.000*	1.00		
Cholesterol (mg/dL)				
Before	129.69±27.5	178.87±51.4	0.000*	<200
After	129.17±29.46	183.23±50.2	0.000*	
P	0.89	0.27		
Triglyceride (mg/dL)				
Before	127.48±70.5	185.33±97.4	0.012*	0-200
After	136.72±61.0	176.87±77.2	0.31	
P	0.41	0.11		
LDL (mg/dL)				
Before	70.34±19.1	108.33±38.3	0.000*	<130
After	65.34±21.4	108.47±39.0	0.000*	
P	0.10	0.96		
HDL (mg/dL)				
Before	35.03±6.3	41.83±6.2	0.000*	35-80
After	38.00±6.23	42.67±6.6	0.007*	
P	0.018*	0.32		
Hemoglobin (g/dL)				
Before	11.10±1.5	11.17±1.4	0.741	14-18
After	11.28±1.6	10.77±1.5	0.205	
P	0.55	0.031*		
Iron (µg/dL)				
Before	116.48±100.8	105.4±81.4	0.644	59-158
After	107.38±66.2	116.87±74.3	0.607	
P	0.66	0.38		
TIBC (µg/dL)				
Before	266.55±70.1	262.60±55.9	0.81	228-428
After	246.86±30.2	251.60±40.1	0.61	
P	0.13	0.20		
Transferrin (mg/dL)				
Before	209.76±58.1	213.40±55.5	0.807	204-360
After	195.21±22.3	198.20±24.9	0.63	
P	0.17	0.11		
Transferrin saturation (%)				
Before	33.34±19.8	33.10±17.2	0.96	15-50
After	36.31±21.0	36.77±19.9	0.96	
P	0.56	0.41		
Ferritin (ng/mL)				
Before	627.03±569.6	621.23±542.8	0.96	22-322
After	401.24±401.8	403.70±396.1	0.98	
P	0.009*	0.005*		
hs-CRP (mg/L)				
Before	0.45±0.9	0.40±0.8	0.0907	<6
After	0.24±0.5	0.6±0.8	0.091	
P	0.16	0.32		

*Statistically significant. LDL=Low-density lipoproteins, HDL=High-density lipoprotein, TIBC=Total iron-binding capacity, hs-CRP=High-sensitivity C-reactive protein, SD=Standard deviation

CKD, its properties are altered and it cannot be effective as in normal conditions.[15] This study showed that Se supplementation can increase HDL levels significantly which is promising news.

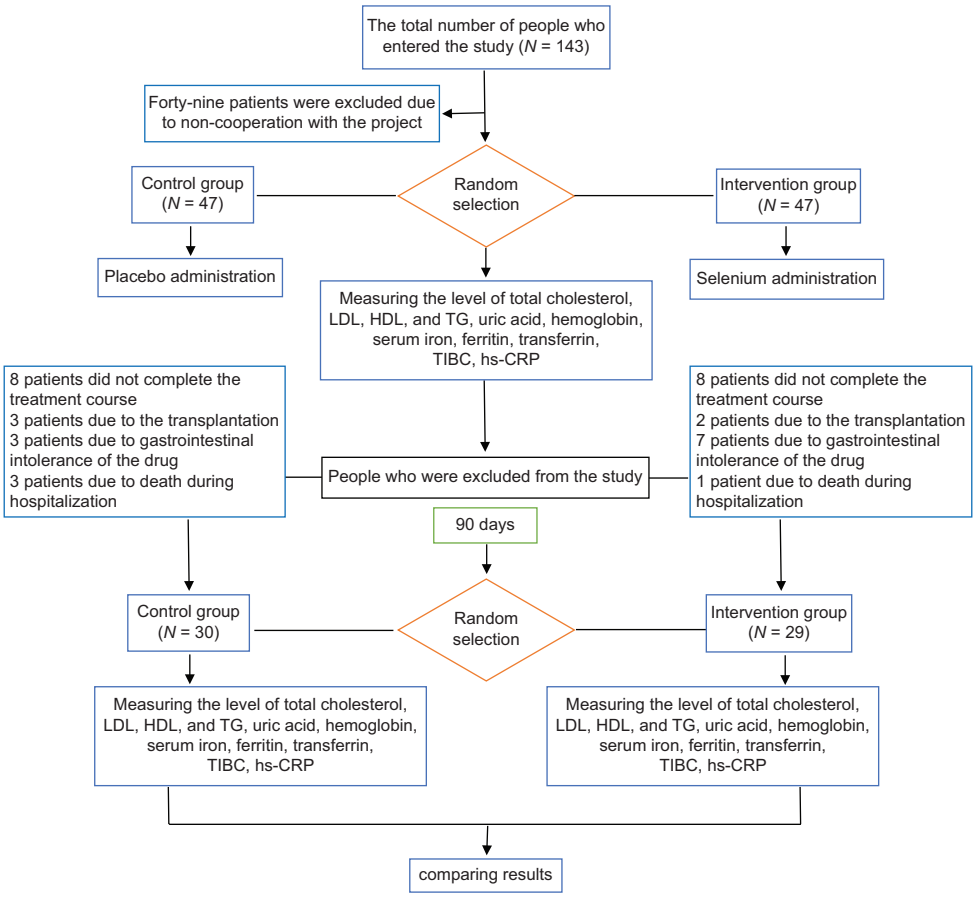

Figure 1: CONSORT diagram of the study protocol, patients' selection and randomization

In addition, it is shown that the UA-to-HDL ratio is a predictive parameter among peritoneal dialysis patients. Ruihua Liu *et al*. showed that higher UA-to-HDL ratio is correlated with higher all-cause mortality in peritoneal dialysis patients, whereas above 65 years old, higher UA-to-HDL ratio is associated with CVD mortality.[16] In our study, this ratio decreased significantly in the case group, while the changes were not significant in the control group. This finding is in accordance with other studies and showed that Se supplementation can affect UA-to-HDL ratio and lower this risk factor among hemodialysis patients.

Other pieces of evidence showed that by decreasing HDL, estimated GFR will decrease concurrently in ESRD patients and its link becomes stronger when HDL decreases more.[17]

In our study, among all measured biomarkers two were out of range in both groups; hemoglobin which was below the normal range, and ferritin which was higher than normal. At the end of the study, ferritin reduced significantly in both groups, but still, it was higher than the normal range. Hemoglobin slightly increased in the case group, however, it decreased significantly in the control group. Increasing hemoglobin is beneficial, but medications such as erythropoiesis-stimulating agents which were used to achieve this, had side effects namely HTN, seizure, and clotting Se supplementation has the potential to increase hemoglobin without these side effects.[18,19]

In ESRD patients, hs-CRP has been proven to be a strong predictor of both cardiovascular and all-cause mortality and is associated with oxidative stress, vascular calcification, and endothelial dysfunction. Hs-CRP is a biomarker of inflammation.[20] It is shown that elevated hs-CRP is independently associated with CVD among dialysis patients.[21] Furthermore, higher longitudinal serum hs-CRP level and its elevated trend over time were predictive of worse prognosis among peritoneal dialysis patients.[22] In our study, however hs-CRP was not out of range in both groups, but after the intervention finished, it decreased in the case group and increased in the control group. None of these changes were statistically significant, but they may pave the way to design new studies to investigate the effect of Se supplementation on hs-CRP levels.

Our study showed that Se supplementation can affect biomarkers which are predictors of CVD mortality and all-cause mortality among ESRD patients. However, the

main limitation of our study was that selenium levels were not measured either at the beginning or at the end; And the baseline levels of selenium in each of the study groups may have influenced the effect of selenium supplementation on the studied biomarkers.

Authors' Contribution

S. Badri, S. Vahdat, S. Seirafian, and M. Pourfarzam developed the idea of research and criticized the findings. S. Assarzadeh recruited and followed the patients. All authors contributed in manuscript preparation and revision.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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