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Original Articles

Selenium supplementation improves the nutritional status of hemodialysis patients: a randomized, double-blind, placebo-controlled trial†

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ABSTRACT

Background. Malnutrition is highly prevalent in hemodialysis (HD) patients. These patients have high levels of oxidative stress and inflammation which can subsequently induce malnutrition. Selenium levels have been found to be decreased in HD patients. As selenium deficiency leads to oxidative stress and inflammatory response, the aim of this study was to evaluate the effects of selenium supplementation on oxidative and inflammatory markers and the nutritional status of HD patients.

Methods. In this randomized double-blind placebo-controlled trial, 80 patients on stable HD for at least 3 months without any acute illness or active infections were randomly allocated to two equal groups to receive one selenium (200 μg) or placebo capsule daily for 12 weeks. Serum levels of lipoproteins, malondialdehyde (MDA), interleukin-6 (IL-6), high-sensitivity C-reactive protein (HSCRP), homocysteine, ferritin and transferrin as well as the subjective global assessment (SGA) score, malnutrition–inflammation score (MIS) and hemoglobin (Hb) levels were measured at the baseline and at the end of the treatment phase. The primary outcome was a change in the nutritional status measured by the SGA score from the baseline towards the end of the treatment phase of the study.

Results. The SGA score and MIS decreased significantly in the selenium group compared to the placebo group ($P < 0.001$ for both). Moreover, serum levels of MDA decreased significantly in the selenium group compared with increasing levels in the placebo group ($P < 0.001$). Selenium supplementation also hindered an increase in IL-6 levels compared with the placebo group ($P = 0.016$). There were no significant differences between the selenium and placebo groups in terms of changes in serum levels of lipoproteins, HSCRP, homocysteine, ferritin and transferrin or Hb levels.

Conclusions. This study shows that selenium may be an effective complementary supplement for reducing the severity of malnutrition in HD patients through alleviating oxidative stress and inflammation.

INTRODUCTION

Malnutrition or insufficient protein-calorie intake is highly prevalent in hemodialysis (HD) patients [1]. Protein-energy wasting and inflammation are concurrent conditions in HD patients and are associated with poor prognosis [1]. Hence, the term malnutrition–inflammation complex syndrome (MICS) was used to comprise both malnutrition and inflammation, regardless of the original causes [1, 2]. MICS is considered as one of the main causes of atherosclerotic cardiovascular disease (CVD), hospitalization and increased mortality in HD patients [1].

Among the contributing factors to the pathogenesis of MICS in HD patients, high oxidative stress is considered to be one of the most important ones [3, 4]. High oxidative stress in HD patients results from increased production of oxidative compounds and impaired antioxidant defense mechanisms [5–7]. Selenium is an essential trace element with known antioxidant properties [8, 9]. It acts as a cofactor for the reduction in important antioxidant enzymes like glutathione peroxidase [10]. Several studies have demonstrated that HD patients have low levels of selenium compared with healthy controls, and deficiency of this trace element may contribute to increased oxidative stress and inflammation in HD patients [10–13]. Furthermore, strong positive correlations between levels of selenium and nutritional markers such as serum albumin have been reported [14, 15]. Therefore, selenium deficiency may also contribute to malnutrition in HD patients [11]. So far, a few small non-controlled trials have shown the efficacy of selenium supplementation in reducing oxidative stress markers in HD patients [6]. However, no clinical study has ever evaluated the efficacy of selenium supplementation on improving clinical outcomes such as malnutrition in these patients. Therefore, we performed this trial to evaluate the efficacy of selenium supplementation on improving the nutritional status of HD patients. Furthermore, to delineate its possible mechanisms of action, we evaluated the effects of selenium supplementation on serum levels of malondialdehyde (MDA) as a surrogate marker for oxidative stress and on serum levels of interleukin-6 (IL-6) and high-sensitivity C-reactive protein (HSCRP) as surrogate markers for inflammation.

MATERIALS AND METHODS

This randomized, double-blind, placebo-controlled, two-arm parallel trial was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The Ethics Committee of Shiraz University of Medical Sciences reviewed and approved the protocol of this study. Eligible participants were 18- to 80-year-old patients who were under regular HD in Faghihi Hospital Hemodialysis Center for 3 months or more. Exclusion criteria were pregnancy, taking antioxidant supplements including vitamin E, vitamin C, lipoic acid, omega-3 fatty acids, soy extracts and green-tea preparations or immunosuppressive medications within 2 months prior to enrollment in the study, hospitalization in the previous month before the onset of the trial, or having active infection.

Sample size was determined according to the subjective global assessment (SGA) score in a previous study in malnourished HD patients [16]. A sample size of 25 patients per group was obtained with a mean difference of 0.8, an SD of 1 and a probability of 80% at the predetermined level of $\alpha = 0.05$. While considering 15 dropouts in each group, the final sample size was determined to be 40 patients per group.

After screening all of the 280 patients under regular HD in Faghihi Hospital Hemodialysis Center, 80 stable patients were found to be eligible for enrollment and gave their informed consent to participate in this trial. These participants were dialyzed three times a week by low-flux dialyzer with polysulfone/polyamide membranes, reverse osmosis purified water and bicarbonate-containing dialysate. These patients were randomly assigned in a 1:1 ratio into two groups:

(i) The patients in the first group received one capsule of selenium in the form of selenium yeast (200 μg) daily for 12 weeks.

(ii) The patients in the second group received one capsule of placebo daily for 12 weeks.

Blocked randomization with a fixed block size of four was performed by one of the investigators who had no clinical involvement in the study using Random Allocation Software [17]. All selenium and placebo capsules were provided by Shiraz School of Pharmacy in prepacked bottles numbered for each patient according to the randomization sequence. Each patient was assigned to an order number and received the selenium or placebo in the corresponding prepacked bottles. The placebo and selenium capsules were completely similar in size, weight, color and taste. All of the patients, clinical investigators, including the one who administered SGA questionnaires, and other health care staff were blinded to the treatment assignment.

Selenium has a narrow window of the therapeutic index. The maximum recommended allowance dose for selenium is 400–450 μg/day. As the baseline selenium levels of the patients were not measured in this study, in order to maintain the patients' safety and reduce the chance of selenium toxicity, the dose of selenium supplementation was chosen to be 200 μg/day. Moreover, in support of choosing this dose, a 3-month treatment of HD patients with the same dose of oral selenium has been demonstrated to be safe and effective in restoring levels of selenium and in attenuating oxidative DNA damage in a study by Zachara *et al.* [18].

SGA is a comprehensive nutritional assessment tool that has several strengths: it is inexpensive and rapid to conduct, can be easily implemented in different disciplines, needs no laboratory evaluation and has been shown to be valid and

reliable in HD patients [19, 20]. Despite these advantages, it should be appreciated that the status of visceral proteins such as albumin is not well assessed by SGA. To compensate for this problem, the malnutrition–inflammation score (MIS) has been developed that incorporates the serum laboratory markers of malnutrition with SGA and is suggested to be a better indicator of MICS [19, 21, 22]. Therefore, in this study, the nutritional statuses of all patients were assessed by both SGA and MIS. At the baseline, the questions of the SGA questionnaire were read to the patients and completed in person by the main investigator of this study who is an experienced nutritionist working with HD patients regularly. The questions of SGA questionnaire were also asked by the same person at the end of the treatment phase. Furthermore, the physical examinations were done by the same person at the baseline and at the end of the treatment phase. The SGA questionnaire inquired about any changes in weight (during the preceding 6 months and 2 weeks), dietary intake, gastrointestinal symptoms, functional capacity and an assumed metabolic demand of the underlying disease. The physical examination consisted of loss of subcutaneous fat, muscle wasting and the presence of ankle/sacral edema. Each of these features were rated as A, B or C separately to indicate the degree of malnutrition. Then, the SGA classifications were converted to numerical equivalents: a score of <10 points was regarded as well-nourished; 10–17 points, at risk for malnutrition or mildly to moderately malnourished; and more than 17 points, severely malnourished [23]. MIS consisted of four sections (nutritional history, physical examination, BMI and laboratory values) and 10 components. The first three sections included five components adopted from the original SGA and the fourth MIS section included two laboratory values: serum albumin and transferrin. Each component had four levels of severity, from 0 (normal) to 3 (severely abnormal). The sum of all 10 MIS components ranged from 0 (normal) to 30 (severely malnourished); a higher score reflected a more severe degree of malnutrition and inflammation [21].

Before the onset of the treatment and after the end of the treatment phase of the study, 10 cc blood samples were taken from each patient. The blood was taken from the patient's arm used for HD cannulae just before the beginning of the HD session. The serum was separated by centrifugation at 3000 *g*/min for 5 min and stored at −70°C. Serum levels of MDA (μmol/L), IL-6 (pg/mL), HSCRP (μg/mL), ferritin (ng/mL), transferrin (μg/dL), homocysteine (μmol/L), calcium (mg/dL), phosphate (mg/dL), parathyroid hormone (PTH) (pg/dL), albumin (g/dL), blood urea nitrogen (BUN) (mg/dL) and creatinine (mg/dL) as well as hemoglobin (Hb) levels (g/dL) were measured in all patients at the baseline and at the end of the treatment phase of the study.

Serum concentrations of MDA were measured by the modified thiobarbituric acid method (spectrophotometric method); the intra- and interassay coefficients of variation were 5.5 and 5.9%, respectively [24]. Serum levels of IL-6, PTH, homocysteine, HSCRP and ferritin were measured using highly sensitive ELISA kits (DIAsource Immunoassays SA, Belgium ELISA kits for IL-6; Biomerica, CA, USA ELISA kits for PTH; Axis Shield, UK ELISA kits for homocysteine; IBL, Germany ELISA kits for HSCRP and ferritin); intra- and interassay coefficients of variation were 4.2 and 4.4%, 2.8 and 5.1%, 7 and 9%, 4.1 and 5.8%, and 7.8 and 7.6%, respectively. Other parameters were measured with standard automated techniques. Adverse events were inspected by clinical staff in each dialysis session during the treatment phase of the trial.

Statistical analyses were done using SPSS version 15 (SPSS Inc., Chicago, IL) statistical software package. Normally distributed data were compared between two groups by an independent sample *t*-test; skewed data were compared by the Mann–Whitney *U*-test and categorical data such as sex by χ^2 test. P-values <0.05 were considered statistically significant. The primary outcome of this trial was an absolute change in nutritional statuses of patients measured by the SGA score from the baseline to the end of the treatment phase of the study in an intention-to-treat population.

This trial is registered with Clinicaltrial.gov, number NCT01147354, where the trial protocol could be accessed.

RESULTS

Eligible participants were recruited from March 2009 to June 2009. As demonstrated in the flow diagram of the study (Figure 1), during the treatment phase of the study, 11 patients were excluded in the selenium group and 4 in the placebo group. The reasons for these exclusions are mentioned in the flow diagram. Baseline demographic and laboratory characteristics of patients in both groups are demonstrated in Table 1; no statistically significant differences were observed between these two groups in terms of baseline characteristics. All of the enrolled patients were under regular treatment with erythropoietin and intravenous iron based on our regional HD guideline.

The changes in measured parameters during the treatment phase of the study are mentioned in Table 2. SGA scores and MIS decreased in the selenium group while these scores increased in the placebo group; when changes in these scores were compared between the two groups, decrements in SGA scores and MIS in the selenium group were significantly different from the corresponding increments in the placebo group ($P < 0.001$ for both). Likewise, a decrement in serum levels of MDA was significantly different from the corresponding increment in the placebo group ($P < 0.001$). Moreover, serum levels of IL-6 increased in both groups; however, this increment was significantly lower in the selenium group ($P = 0.016$). Changes in other parameters were not significantly different between two groups.

The frequency of serious adverse events and other adverse events in patients is demonstrated in Table 3. Other adverse events occurred in the first 2 weeks of treatment, and none of them was bothersome enough to compel the patients to quit the treatment.

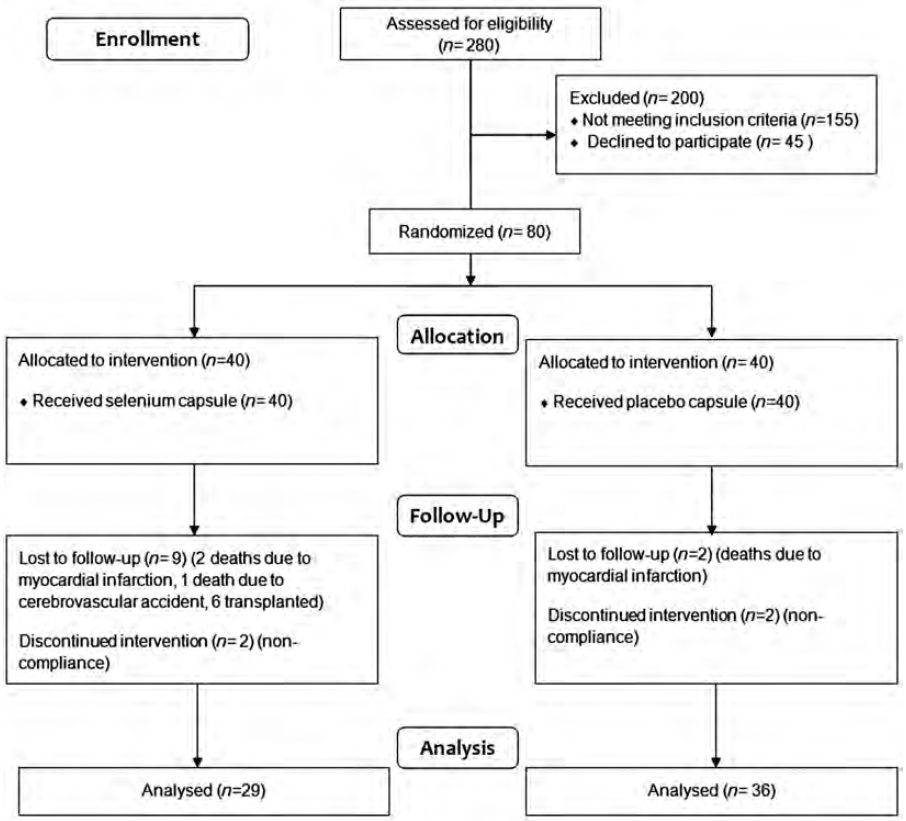

FIGURE 1: Flow diagram of the trial.

DISCUSSION

Our study, for the first time, demonstrated the efficacy of selenium supplementation in improving the nutritional status of HD patients. This effect is probably mediated by inhibiting oxidative stress and inflammation.

High oxidative stress and generalized inflammation are implicated in the pathogenesis of several complications of HD like atherosclerotic CVD, anemia and malnutrition [3, 7, 25]. This high oxidative stress in HD patients results from an imbalance between pro- and antioxidant factors [6, 7]. Among defense mechanisms against oxidative injury, selenium-dependent enzymes like glutathione peroxidase are the most important ones [5, 8, 25]. There are several reports on the deficiency of selenium and its dependent enzymes in HD patients [5, 12, 13, 26]. Furthermore, low levels of selenium in HD patients have been reported to be associated with increased inflammatory markers [27]. There are also reports on a possible association of selenium deficiency with increased risk of malnutrition in HD patients evidenced by significant positive correlations found between low levels of selenium and of nutritional markers such as serum albumin, total muscle mass, triceps skin-fold and mid-arm muscle circumference [11, 14, 15, 26, 28]. Although few interventional studies have demonstrated the beneficial effects of selenium supplementation on reducing oxidative stress markers or increasing the activity of antioxidant enzymes in HD patients [28–32], the potential efficacy of selenium supplementation in improving clinical outcomes like malnutrition in these patients has not been evaluated in any randomized controlled trial so far.

In our study, a decrease in serum levels of MDA in the selenium group was significantly higher than placebo. In an interventional study by Ardalan *et al.* [32], selenium and vitamin E administration to HD patients prevented the iron infusion-induced increase in serum levels of MDA. In another interventional study by Koenig *et al.* [31], selenium supplementation decreased plasma levels of MDA and increased levels of antioxidant enzymes like glutathione peroxidase in HD patients. Furthermore, in a recent interventional study, Zachara *et al.* [18] have demonstrated that HD patients have higher oxidative DNA damage in white blood cells compared with healthy controls, and selenium supplementation could significantly dampen this damage. Moreover, in our study, an increase in serum levels of IL-6 levels was significantly lower in the selenium group than placebo. By regulating the expression of selenoprotein genes, selenium has been shown to inhibit the activation of nuclear factor kappa B (NF-κB) signaling pathway and therefore decrease the production of inflammatory cytokines such as IL-6 [33, 34]. Therefore, based on the findings of our study, the observed beneficial effect of selenium supplementation on improving the nutritional status of HD patients may be partly mediated by the inhibition of oxidative damage and inflammation. However, in this study, changes in serum levels of other inflammatory markers such as HSCRP were not significantly different between two groups. These

Table 1. Baseline demographic characteristics and measured parameters in patients

Demographic characteristics and measured parameters in patients	Selenium	Placebo	P-value
Number	40	40	—
Causes of ESRD (frequency)			
Hypertensive nephropathy	17 (42.5)[a]	17 (42.5)	—
Diabetic nephropathy	14 (35)	11 (27.5)	
Renal stone	1 (2.5)	0 (0)	
Polycystic kidney disease	0 (0)	1 (2.5)	
Pyelonephritis	2 (5)	1 (2.5)	
Glomerulonephritis	1 (2.5)	1 (2.5)	
Unknown	5 (12.5)	9 (22.5)	
Age (years)	50 ± 15.4	55 ± 13	NS
Gender (female)	24 (60)	20 (50)	NS
BMI (kg/m^2)	22.86 ± 4.07	22.37 ± 3.52	NS
Daily Kt/V	1.42 ± 0.26	1.34 ± 0.17	NS
Creatinine (mg/dL)	7.75 ± 2.6	8.5 ± 4.11	NS
BUN (mg/dL)	64.04 ± 21.3	64.9 ± 28.9	NS
Calcium (mg/dL)	8.12 ± 1.1	8.13 ± 0.89	NS
Phosphorus (mg/dL)	5.25 ± 1.8	5.64 ± 1.6	NS
PTH (pg/dL)	84.9 (8.85, 318.97)	96.7 (25.97, 221.6)	NS
Albumin (g/dL)	4.43 ± 0.69	4.1 ± 1.06	NS
SGA score	12 (9, 18)	11 (8.25, 12)	NS
MIS	9 (4.25, 14.75)	8 (5, 10)	NS
MDA (μmol/L)	11.83 ± 3.02	11.56 ± 2.9	NS
IL-6 (pg/mL)	33.55 (8.37, 53.45)	14.55 (0.5, 53.17)	NS
HSCRP (μg/mL)	4.5 (1.72,19.97)	6.7 (2.75, 26.77)	NS
TG (mg/dL)	104.53 ± 58.59	121.5 ± 60.73	NS
Total cholesterol (mg/dL)	155.81 ± 33.77	163.5 ± 39.31	NS
LDL (mg/dL)	88.09 ± 27.88	89.45 ± 34.3	NS
HDL (mg/dL)	46.08 ± 17.1	49.75 ± 14.21	NS
Homocysteine (μmol/L)	23.7 ± 10.38	24.45 ± 8.25	NS
Ferritin (ng/mL)	819.4 (439.95, 1180)	838.9 (468.52, 1048.5)	NS
Total iron binding capacity (μg/dL)	315 (204, 454)	303 (147, 474.75)	NS
Hb (g/dL)	9.94 ± 2.28	10.4 ± 2.22	NS

NS, not significant.
[a]Categorical data are expressed as number (%), continuous data with normal distribution as means ± SDs and continuous data with skewed distribution as median (IQR).

differences may reach significance levels in studies with larger sample sizes and longer durations.

In addition to its antioxidant and anti-inflammatory properties, the observed beneficial effects of selenium on the nutritional status may be attributed to its effects on the digestion and absorption of fat, nutrient utilization, decreasing ketone bodies (as appetite suppressants) and improving insulin effects [35–38].

Table 2. Effect of selenium supplementation on levels of measured parameters in patients

Measured parameters	Selenium group	Placebo group	P-value
SGA score	−3.89 ± 3.2 [−5.13 to −2.65][a]	1.35 ± 3.01 [0.3–2.4]	<0.001
MIS	−4.17 ± 4.2 [−5.81 to −2.54]	0.7 ± 3.71 [−0.58 to 2]	<0.001
MDA (μmol/l)	−1.2 (−3.17, −0.45) [−2.41 to −1.16]	0.6 (0.01, 2.22) [0.47–1.86]	<0.001
IL-6 (pg/mL)	6.05 (−20.4, 50.8) [−61.4 to 89.68]	22.95 (0.92, 1978.2) [336.33–1218.3]	0.016
HSCRP (μg/mL)	−0.85 (−2.47, 5.25) [−1.99 to 16.46]	1.3 (−17.7, 4.52) [−13.69 to 5.08]	NS
TG (mg/dL)	14.5 (−2.5, 54.25) [3.06–50.55]	23 (−12, 54) [−7.25 to 36.28]	NS
Total cholesterol(mg/dL)	−13.7 ± 50.4 [−34.09 to 6.63]	−8.02 ± 59.6 [−28.51 to 12.45]	NS
LDL (mg/dL)	−15.2 ± 45.27 [−33.5 to 3.07]	−5.44 ± 53.86 [−23.94 to 13.06]	NS
HDL (mg/dL)	7.7 ± 26.1 [−2.16 to 17.7]	0.69 ± 23.5 [−7.26 to 8.64]	NS
Homocysteine (μmol/L)	−6.04 ± 9.04 [−9.48 to −2.59]	−2.75 ± 10.02 [−6.14 to 0.64]	NS
Ferritin (ng/mL)	23 (−107, 216.45) [−26.67 to 168.58]	−31.4 (−153.65, 124.35) [−194.55 to 38.5]	NS
Total iron-binding capacity (μg/dL)	−15 (−276, 103.5) [−322.35 to −0.74]	6 (−177, 162) [−88.11 to 128.17]	NS
Hb (g/dL)	−0.23 ± 2.04 [−1.01 to 0.53]	−0.14 ± 2.29 [−0.9 to 0.62]	NS
Albumin (g/dL)	0.61 ± 1.14 [0.17–1.05]	0.4 ± 1.09 [−0.01 to 0.81]	NS

NS, not significant.
[a]Continuous data with normal distribution are expressed as means ± SDs [95% confidence interval] and continuous data with skewed distribution as median (IQR) [95% confidence interval].

Table 3. Adverse events in patients

Adverse events		Selenium group	Placebo group
Serious adverse events	Death due to myocardial infarction	2[a]	2
	Death due to cerebrovascular accident	1	0
Other adverse events	Dyspepsia and abdominal pain	2	3
	Nausea and vomiting	2	0

[a]Number of patients with adverse events.

The beneficial effect of selenium supplementation on the nutritional status of patients with chronic diseases was also observed in a randomized interventional study by Federico *et al.* [39]; in this interventional study, aggravation of the nutritional status was prevented in patients with cancer of the digestive tract who received selenium and zinc supplementation compared with those who received placebo.

CVD is the main cause of mortality in HD population [4, 6]. Malnutrition, inflammation and oxidative stress are all proposed to contribute to the pathogenesis of CVD in HD patients through mediation of vascular injury and endothelial dysfunction [4, 6, 40]. Surrogate markers of malnutrition and inflammation such as MIS, SGA score and serum levels of IL-6 have been demonstrated to be correlated with the prospective mortality rate in HD patients in several studies [21, 22, 41, 42]. Moreover, antioxidant therapies like vitamin E and *N*-acetylcysteine have been shown to be effective in reducing CVD events in HD patients [43, 44]. Therefore, selenium supplementation that has been demonstrated to be effective in hampering the surrogate markers of malnutrition, inflammation and oxidative stress in our study could potentially reduce CVD and its resultant mortality in HD patients. However, this claim needs to be further evaluated in future studies with larger sample sizes and longer durations.

Selenium has a low therapeutic index, and toxicity may occur with its high-dose supplementation; adverse effects of selenium toxicity include brittle hair and nails and their loss, dermatitis, pulmonary edema, neurotoxicity, nausea and vomiting [12, 45]. Except for gastrointestinal disturbances in few patients, none of the other adverse effects of selenium toxicity was observed in this trial. A few cardiovascular deaths also occurred in both selenium and placebo groups; however, these deaths are probably due to higher prevalence of CVDs in HD population. The low incidence of adverse events in this study may be due to the administration of lower dose of selenium (200 μg/day) compared with its maximum allowance dose (400–450 μg/day) [12]. Other trials which used similar doses of selenium in HD patients also did not report the adverse events of selenium toxicity [18, 30, 32]. However, due to short duration and low sample size of these trials as well as our trial, selenium supplementation in HD patients could not be claimed safe.

The main limitation of our study, and interpretation of its results, is the lack of the selenium measurement at the baseline and at the end of the treatment phase. Without measuring these levels, it is not known to what extent the differences in the baseline selenium levels might have impacted the therapeutic effect of the selenium supplementation; therefore, it is impossible to say that the selenium supplementation was actually successful. Low sample size and short duration are other limitations of our study.

In conclusion, our study for the first time demonstrated the efficacy of selenium supplementation in improving the nutritional status of HD patients in short term. This perceived effect may be mediated by hampering oxidative stress and inflammation. Therefore, selenium supplementation may be considered as an addition to the current therapeutic remedies for malnutrition in HD patients. However, further multicenter trials with larger sample sizes are needed to confirm its efficacy and safety in the long term and also to delineate its possible mechanisms of action.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to declare.

(See related article by Thompson and Tonelli. Selenium for malnutrition in hemodialysis patients: have we considered all of the elements? *Nephrol Dial Transplant* 2013; 28: 498–500.)

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