

The Effect of Selenium Supplementation on Acute Phase Reactants and Thyroid Function Tests in Hemodialysis Patients

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Background: Selenium deficiency is a common problem in patients with chronic kidney disease (CKD). This micronutrient has anti-inflammatory and anti-oxidant effects. Selenium is also found in high concentrations in the thyroid gland.

Objectives: To determine the effect of selenium supplementation on thyroid function tests and acute phase reactants in hemodialysis patients.

Patients and Methods: In this double-blinded randomized clinical in 3 months, 64 hemodialysis patients with selenium deficiency were divided into experimental (received selenium supplementation; 32 cases) or control group (received placebo; 32 cases). Erythrocyte sedimentation rate (ESR), ferritin, quantitative C-reactive protein (CRP) and thyroid function tests (TFTs) including thyroid stimulating hormone (TSH), T3 resin uptake (T3RU), and free T4 were measured before and after the intervention and compared between experimental and control groups.

Results: At baseline, no significant difference was found between experimental and control groups regarding CRP, ESR and ferritin serum levels. Likewise, after intervention, no significant difference was found between experimental and control groups for CRP (14.77 ± 17.93 vs. 18.29 ± 21.56 mg/L), ESR (32.90 ± 32.62 vs. 33.91 ± 31.15 mm/h) and ferritin (528.6 ± 423.07 vs. 519.52 ± 345.59 ng/mL). At baseline, no significant difference was found between experimental and control groups regarding TFTs. Likewise, after intervention, no significant difference was found between experimental and control groups for TSH (3.7 ± 2.22 vs. 2.84 ± 1.88 μ U/mL), free T4 (7.19 ± 1.98 vs. 7.02 ± 1.87 μ g/dL) and T3RU ($30.04 \pm 2.28\%$ vs. $29.2 \pm 1.98\%$).

Conclusions: Oral selenium supplementation for three months did not have any significant effect on thyroid function tests or acute phase reactants.

Keywords: Renal Failure; Selenium; Thyroid Function Tests; Blood Sedimentation; Ferritins; C-Reactive Protein

1. Background

Enhanced inflammation is well-established in patients with chronic kidney disease (CKD). Several factors have been implicated in such inflammation in patients with CKD including uremic state, elevated serum inflammatory markers, oxidative stress, etc. (1-3). Systemic inflammation has important implications in renal failure and can lead to potentially severe conditions such as premature atherosclerosis. Premature atherosclerosis is one of the main causes of death in hemodialysis patients (4, 5). Some studies suggested that hemodialysis itself increases the production of free radicals (6-8).

In addition to inflammation, malnutrition has been considered as an important determinant factor in clinical outcome of patients with CKD (9, 10). Among various nutritional elements, selenium has been implicated in patients with CKD (11). In fact, there is extensive evidence that selenium level is depleted in patients with CKD, especially those under hemodialysis (4, 5, 12).

Selenium is an important trace mineral in the human

body. This nutrient is an essential part of enzymes of the body's cells against free radicals by participating in the structure of glutathione peroxidase. Free radicals are formed during natural oxygen metabolism process of body and have widespread destructive effects on body. One of the essential functions of selenium is preventing heart disease and elevated blood pressure (13, 14).

Selenium has also important role in the thyroid gland. In fact, the highest concentration of selenium inside the human body (per gram tissue) is found in the thyroid (15). For long time, the association of selenium level and thyroid dysfunction has been studied. This is mainly due to special selenoproteins inside the thyroid gland and activity of thyroid enzyme deiodinase, which requires selenium for its proper function (16). There is evidence that thyroid hormones function and morphology are disturbed in CKD. Abnormal changes reported include reduction in serum level of total and free T3 and T4, increase in rT3 and TSH reduction (17). In fact, hypothy-

roidism has been documented to occur in a higher rate in patients with CKD than general population (18). Considering the abnormal changes in TFTs in patients with CKD, some authors advised mathematical calculations to correct TFTs measurements so that a subnormal free T4 in a non-thyroidal disease would not cause confusion in diagnosing hypothyroidism (19).

2. Objectives

Since micronutrients are important components in metabolism pathways of proteins and enzymes and have many metabolic functions, any changes in their serum level can have profound impact on other important and critical parts of body. In view of the fact that selenium may influence inflammation and thyroid function, we decided to evaluate the role of selenium supplementation regarding any possible changes in inflammatory markers and TFTs in patients with CKD undergoing hemodialysis.

3. Patients and Methods

In this double-blinded clinical trial, 64 consecutive patients presented to out tertiary care center to undergo hemodialysis and six months had passed from hemodialysis initiation were included. Exclusion criteria were acute viral infections in past three months, previous or current diseases of thyroid, taking steroidal and non-steroidal anti-inflammatory drugs, taking vitamins E and C and zinc during two past months prior to the study.

Before hemodialysis, 3 mL of venous blood was obtained. Firstly, serum selenium level was measured. Selenium measurement was performed via atomic absorption analysis using Vapor Generation Accessory (VGA). Normal range was 63 - 160 µg/dL. Patients with low levels of selenium were randomly divided (using random number table) into experimental (32 cases) and control (32 cases) groups. Experimental group received selenium capsules (200 µg/day) for three months, while control group received placebo capsules for the same period.

For laboratory markers, 3 mL of venous blood was obtained before hemodialysis. This was performed twice first at the start of study and again after three months. The following markers were measured; ESR (erythrocyte sedimentation rate), ferritin, quantitative C-reactive protein (CRP) and thyroid function tests (thyroid-stimulating hormone (TSH), T3 resin uptake (T3RU) and free T4).

After completion of hemodialysis, weight was measured with light clothing using a weight scale with precision of 1 kg. Height was also measured without shoes by a meter installed on the wall with precision of 1 cm.

Data was analyzed using SPSS software for Windows (ver. 20.0) (SPSS Inc., Chicago, IL). For description, mean and standard deviation (\pm SD) were used. To compare the data between experimental and control groups, independent t-test, paired t-test, Wilcoxon test and Mann-Whitney test were applied. Analysis of covariance (ANCOVA) was also applied. After normal distribution of dependent variables and ascertaining proportional odds, ordinal regression was used, otherwise logistic regression was applied. Significance level was set at 0.05.

The study protocol was confirmed by the Ethics Committee of Research of Kermanshah University of Medical Sciences, Kermanshah, Iran. Written informed consent was obtained from patients. All data were kept confidential. Both selenium and placebo were delivered to patients free of charge. In case of detecting any abnormality in laboratory tests, patients were referred to related specialists.

4. Results

Mean (\pm SD) age of experimental and control groups were 57.34 (\pm 13.23) and 59.53 (\pm 14.68) years, respectively ($P = 0.53$). There were 15 males (46.9%) in experimental group and 17 females (53.1%) in the control group. The proportion of males and females in control group was the same. Mean (\pm SD) body mass index (BMI) values in experimental and control groups were 23.78 (\pm 4.83) and 24.46 (\pm 3.68) kg/m², respectively ($P = 0.54$). Mean (\pm SD) serum selenium levels before the intervention in experimental and control groups were 32.81 (\pm 10.5) and 39.09 (\pm 13.18) µg/dL, respectively ($P = 0.049$). ANCOVA showed that by controlling selenium effect before the intervention between the two groups, selenium change after the intervention was significant ($P < 0.001$). Mean (\pm SD) selenium levels after the intervention in experimental and control groups were 182.16 (\pm 42.4) and 51.16 (\pm 36.37) µg/dL, respectively.

Table 1 presents the comparison between acute phase reactants measured at baseline and after three months. As seen, selenium supplementation did not have any significant effect on acute phase reactants. In Table 2, mean \pm SD values of thyroid function tests are presented at baseline and after intervention.

Table 1. Comparison Between Acute Phase Reactants Measured at Baseline and After Three Months Between Experimental and Control Groups ^{a,b}

	Baseline		P Value	After Three Months of Intervention		
	Experimental	Control		Experimental	Control	P Value
CRP, mg/L	12.44 \pm 17.17	10.09 \pm 8.84	0.49	14.77 \pm 17.93	18.29 \pm 21.56	NS
ESR, mm/h	34.5 \pm 33.8	38.5 \pm 35.4	> 0.05	32.90 \pm 32.62	33.91 \pm 31.15	0.9
Ferritin, ng/mL	531.61 \pm 432.49	494.58 \pm 332.006	> 0.05	528.6 \pm 423.07	519.52 \pm 345.59	0.25

^a Abbreviations: CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

^b Values are presented as Mean \pm SD.

Table 2. Comparison of Mean \pm SD Values of Thyroid Function Tests at Baseline and After Intervention Between Experimental and Control Groups^a

	Baseline			After 3 Months of Intervention		
	Experimental	Control	P value	Experimental	Control	P value
TSH, μU/mL	3.47 \pm 2.32	2.8 \pm 1.83	> 0.05	3.7 \pm 2.22	2.84 \pm 1.88	0.29
Free T4, μg/dL	7.35 \pm 1.50	7.01 \pm 1.55	> 0.05	7.19 \pm 1.98	7.02 \pm 1.87	0.98
T3RU, %	30.5 \pm 3.08	29.62 \pm 3.04	> 0.05	30.04 \pm 2.28	29.2 \pm 1.98	0.19

^a Abbreviations: T3RU: T3 resin uptake, TSH: thyroid stimulating hormone.

5. Discussion

We studied the effects of selenium supplementation in hemodialysis patients who had low serum levels of selenium. According to the obtained results, although serum selenium level increased significantly after supplementation and was higher after three months in experimental group compared to control group, selenium supplementation did not have any significant effect on acute phase reactants or TFTs. At baseline, mean CRP level was higher in experimental group than control group. After three months, we observed increase in CRP level in the both groups, but change in CRP level in experimental group was less prominent than that of control group, though the difference was insignificant.

Salehi et al. (11) studied 80 hemodialysis patients in a randomized double-blind trial and followed them for three months to determine the effects of selenium supplementation on inflammatory markers. Similar to our study, used selenium dosage was 200 μ g per day. They reported no significant differences between selenium and placebo groups regarding changes in serum levels of lipoproteins, high-sensitivity CRP, homocysteine, ferritin and transferrin. In their study, mean ferritin level in selenium group was 819.4 ng/mL with an interquartile range of 439.95 to 1180, which changed by a mean of 23 ng/mL (95% CI = -26.67 to 168.58) and was not statistically different from the placebo group. Mean HS-CRP in selenium group was 4.5 with an interquartile range of 1.72 to 19.97. After supplementation, HS-CRP showed a mean decrease by 0.85 μ g/mL, which did not show significant difference to the control group. The only inflammatory marker decreased significantly in that study in selenium group was IL-6. In support of the concept of beneficial effects of selenium on oxidative stress and inflammation, previous reports recommended selenium supplementation in hemodialysis patients (20, 21). In another trial (22), 45 mild, moderate and severe CKD patients of at least six-month duration were studied to find out the effect of selenium supplementation on red blood cell glutathione peroxidase (GSH - Pxs) enzyme activity. Selenium supplementation (200 μ g daily) was given for three months. The authors reported that this intervention was effective in increasing mean GSH-Pxs level as well as plasma selenium level significantly regardless of CKD severity.

We did not find any study about the effect of selenium supplementation on thyroid function in patients with CKD. There is only one study performed on patients with acute renal failure (23). In the mentioned study, 28 cases with acute renal failure and multiple organ dysfunctions were followed during hospitalization. The authors reported that thyroid hormone levels were reduced without an increase in TSH. They observed T4 increase after selenium supplementation. The role of kidney disease and its effect on TFTs is supported further by reports which observed improvement in thyroid hormones and morphology after kidney transplantation (17).

We had some limitations in this study. Firstly, we had a relatively low sample size. We recommend to perform future studies with larger sample sizes to address controversy in the literature. In addition, the study period was relatively short. Therefore, we recommend to perform future studies in longer periods on more patients. Besides, various factors could affect acute phase reactants like infections, which were not able to monitor in this study. It is recommended to control confounding variables, which can adversely affect acute phase reactants such as CRP and ESR to yield better assessment of selenium effect on these inflammatory markers.

The effect of selenium on inflammatory markers and TFTs in hemodialysis patients is controversial. According to our findings, selenium supplementation via oral route for three months did not have any significant effect on these laboratory markers.

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Authors' Contributions

Study concept and design: Hamid Reza Omrani. Acquisition of data: Kanan Nikseresht. Analysis and interpretation of data: Kanan Nikseresht. Drafting of the manuscript: Mehrali Rahimi. Critical revision of the manuscript for important intellectual content: Hamid Reza Omrani. Statistical analysis: Kanan Nikseresht. Administrative, technical and material supports: Mehrali Rahimi. Study supervision: Hamid Reza Omrani.

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