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Effect of Selenium Supplementation on Glycemic Control and Lipid Profiles in Patients with Diabetic Nephropathy

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Abstract To our knowledge, data on the effects of selenium supplementation on glycemic control and lipid concentrations in patients with diabetic nephropathy (DN) are scarce. The current study was done to determine the effects of selenium supplementation on glycemic control and lipid concentrations in patients with DN. This was a randomized double-blind placebo-controlled clinical trial in which 60 patients with DN were randomly allocated into two groups to receive either 200 μg of selenium supplements ($n=30$) or placebo ($n=30$) daily for 12 weeks. Blood sampling was performed for the quantification of glycemic indicators and lipid profiles at the onset of the study and after 12 weeks of intervention. Selenium supplementation for 12 weeks resulted in a significant decrease in serum insulin levels ($P=0.01$), homeostasis model of assessment-estimated insulin resistance (HOMA-IR) ($P=0.02$), homeostasis model of assessment-estimated B cell function (HOMA-B) ($P=0.009$) and a significant rise in plasma glutathione peroxidase (GPx) ($P=0.001$) compared with the placebo. Taking selenium supplements had no significant effects on fasting plasma glucose (FPG), quantitative insulin sensitivity check index (QUICKI) and lipid profiles compared with the placebo. Overall, our study demonstrated that selenium supplementation for 12 weeks among patients with DN had beneficial effects on plasma GPx, serum insulin levels, HOMA-IR, and HOMA-B, while it did not affect FPG, QUICKI, and lipid profiles.

Keywords Selenium · Supplementation · Diabetic nephropathy · Metabolic status

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Introduction

Diabetic nephropathy (DN) remains a main cause of morbidity and mortality in the diabetic population and is the leading cause of end-stage renal disease, hence kidney transplantations [1]. It affects approximately 25–40 % of type 1 and type 2 diabetic patients [2]. Although type 2 diabetes mellitus (T2DM) is clearly an insulin-resistant state, patients who develop DN have been shown to be more insulin resistant than those who do not [2]. Several studies demonstrated the important role of hyperglycemia and insulin resistance in the pathogenesis of DN [3, 4].

In recent years, the use of selenium supplements has increased in many countries due to the perception that selenium may reduce the risk of chronic diseases and their complications. In addition, some studies have indicated that circulating levels of selenium and glutathione peroxidase (GPx) were low in diabetic patients with macroalbuminuria [5, 6]. Selenium depletion may result in the development of vascular complications and microalbuminuria in diabetic patients through increasing oxidative stress [7]. Dietary sources of selenium are nuts, cereals, meat, mushrooms, fish, and eggs [8]. Selenium is an important component of the enzymes that protect cells

from the adverse effects of reactive oxygen species and free radicals [9–11]. In addition, selenium is involved in the production of thyroid hormones and has been shown to contain anti-inflammatory effects [12]. Although the beneficial effects of selenium supplementation on glycemic status and lipid concentrations in patients with cervical intraepithelial neoplasia grade 1 (CIN1) [13], gestational diabetes [14] and polycystic ovary syndrome (PCOS) [15–17] have been reported, limited data are available examining such effects in patients with DN. Some studies have reported the beneficial effects of selenium intake on markers of insulin metabolism in animal models [18, 19]. In a 6-week supplementation with 200 μg/day of selenium, a significant decrease in serum insulin concentrations, homeostasis model of assessment-insulin resistance (HOMA-IR), and triglyceride levels was observed in women with central obesity; however, it did not affect other lipid profiles [20]. Selenium intake with a dosage of 200 μg/day among patients with T2DM for 3 months did not affect circulating levels of insulin [21].

The use of selenium may improve glycemic status and lipid profiles through regulating expression of genes responsible for the synthesis of enzymes involved in the carbohydrate metabolism [22] and the inhibition of inflammatory cytokines [23]. These mechanisms might suggest the importance of selenium administration in DN patients. To our knowledge, no reports are available evaluating the effects of selenium administration on glycemic control and lipid concentrations in diabetic patients with overt proteinuria. This clinical trial was done to investigate the effects of selenium supplementation on glycemic control and lipid concentrations in patients with DN.

Subjects and Methods

Participants

In this randomized double-blind placebo controlled clinical trial, we included patients with DN, with a proteinuria level of >0.3 g/24 h, aged 45–85 years old who were referred to Akhavan Clinic in Kashan, Iran from March 2015 to June 2015. We defined DN as diabetic renal disease with proteinuria, with or without elevation of serum creatinine levels [24]. The exclusion criteria were as follows: consuming selenium supplements within 3 months before beginning of the study, history of hospital admission within 3 months, bacteriuria, hematuria, urinary tract infection, malignancy, and/or liver cirrhosis. To calculate sample size, we used the standard formula suggested for clinical trials by considering type one error (α) of 0.05 and type two error (β) of 0.20 (power = 80 %). Based on a previous study [25], we used 2.76 as SD and 2.20 as the difference in mean (d) of HOMA-IR as the key variable. Based on this, we needed 25 subjects in each group. Considering five dropouts in each group, the final sample size was determined to be 30 patients per group. Written informed consent was taken from all patients and the research protocol was approved by the ethics committee on human experimentation of Kashan University of Medical Sciences (KUMS). This trial was registered in the Iranian website for registration of clinical trials (http://www.irct.ir.IRCT2015060622562N1).

Study Design

At the onset of the study and after stratification for sex, dose of medications, duration of diabetes, type of diabetes, BMI, and age, 60 patients with DN that met the inclusion criteria were randomly allocated into two groups to receive either 200 μg/day of selenium supplements [26] (n = 30, 15 males and 15 females) or placebo (n = 30, 15 males and 15 females) per day for 12 weeks. Selenium compounds commonly exist in the oxidation states −2, +2, +4, and +6; in the current study, we used selenium supplements as selenium yeast. Selenium supplements and its placebos were manufactured by Nature Made Co (California, USA) and Barij Essence Co (Kashan, Iran), respectively. Randomization was done using a random number table by one of the investigators who had no clinical involvement in the study. Patients were asked to maintain their routine diet and physical activity during the intervention, and not to receive any supplements that might influence their nutritional status during the 12-week intervention. Compliance to the consumption of selenium supplements and placebos was evaluated through asking patients to return the medication containers and receiving short messages on cell phones by patients. The report of daily 3-day food records and three physical activity records (one weekend day and two weekdays) was collected at study baseline, end-of-trial, and throughout the trial (week 3, 6, and 9 of the intervention). Daily macro- and micro-nutrient intake was analyzed by nutritionist IV software (First Databank, San Bruno, CA).

Assessment of Anthropometric Measures

Body weight and height were quantified in a fasting status using a digital scale (Seca, Hamburg, Germany) at the beginning and end of the study. Body mass index (BMI) was determined by weight and height measurements (weight (kg)/height (m^2)).

Assessment of Outcomes

Primary outcome variables were markers of insulin metabolism in the current study. In our study, secondary outcome variables were fasting plasma glucose (FPG), serum triglycerides, cholesterol-, VLDL-, LDL-, HDL-cholesterol, serum creatinine, and blood urea nitrogen (BUN) concentrations. At pre- and post-intervention, 10 mL blood samples were obtained from each patient at Kashan reference laboratory in an early morning after

an overnight fast. FPG and lipid profiles were measured on the day of blood collection. Blood samples were immediately centrifuged (Hettich D-78532, Tuttlingen, Germany) at 3500 rpm for 10 min to separate serum. Then, the samples were stored at −70°C before analysis at the KUMS reference laboratory. Available commercial kits were used to determine FPG, serum triglycerides, cholesterol-, VLDL-, LDL-, HDL-cholesterol, creatinine, and BUN concentrations (Pars Azmun, Tehran, Iran). All inter- and intra-assay coefficient of variations (CVs) for FPG, lipid concentrations, creatinine, and BUN were less than 5 %. Circulating levels of insulin were assessed by the use of available ELISA kit (Monobind, California, USA) with intra- and inter-assay CVs of 3.0 and 5.3 %, respectively. To determine the HOMA-IR, estimated β cell function (HOMA-B), and the quantitative insulin sensitivity check index (QUICKI), we used suggested formulas [26]. GPx activity was determined using ELISA kit (Bioassay Technology, Shanghai, China) with intra- and inter-assay CVs of 7.4 and 9.1 %, respectively.

Statistical Methods

Kolmogorov-Smirnov normality tests were done to evaluate the normal distribution of variables. The analyses were conducted based on intention-to-treat (ITT) principle. To detect differences in anthropometric measures as well as in dietary intakes between the two groups, we used independent sample Student's *t* test. For comparison of categorical variables, the Pearson chi-square test was used. To determine the effects of selenium administration on glycemic control and lipid concentrations, we used one-way repeated measures analysis of variance. To identify within-group changes (before and after 12 weeks of intervention), we applied paired-samples *t* tests. Adjustment for differences in baseline measures of biochemical indicators, age, and BMI were performed by analysis of covariance (ANCOVA) using general linear models. A P value of <0.05 was considered statistically significant. All statistical analyses were done by the use of the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA).

Results

Among patients in the selenium group, 4 patients [withdrawn due to personal reasons ($n=4$)] and in the placebo group, 4 persons [withdrawn due to personal reasons ($n=4$)] were excluded (Fig. 1). Finally, 52 participants [selenium ($n=26$) and placebo ($n=26$)] completed the trial. However, as the analysis was done based on ITT principle, all 60 patients (30 in each group) were included in the final analysis.

Mean age, baseline weight, and BMI of study participants, duration of DM, and the consumption of antidiabetic and antilipidemic drugs were not statistically different between the two groups (Table 1). Baseline weight and BMI as well as their means after trial were not significantly different comparing the two groups.

Based on the 3-day dietary records obtained at study baseline, end-of-trial, and throughout the study (week 3, 6, and 9 of the intervention), we found no significant difference in dietary macro- and micro-nutrient intakes between the two groups (Data not shown).

The use of selenium supplements for 12 weeks resulted in a significant decrease in serum insulin levels (−3.1 ± 4.6 vs. + 0.5 ± 6.2 μIU/mL, $P=0.01$), HOMA-IR (−0.9 ± 1.4 vs. +0.1 ± 1.7, $P=0.02$), HOMA-B (−11.3 ± 16.3 vs. +2.3 ± 22.0, $P=0.009$) and a significant rise in a significant rise in GPx (+2.3 ± 21.7 vs. -27.7 ± 35.2 U/mL, $P=0.001$) compared with the placebo (Fig. 2).

Taking selenium supplements had no significant effects on FPG, QUICKI, lipid profiles, creatinine, and BUN compared with the placebo (Table 2). Within-group changes exhibited significant reductions in serum insulin ($P=0.001$), HOMA-IR ($P=0.002$), HOMA-B ($P=0.001$), BUN ($P=0.03$) and a significant increase in QUICKI ($P=0.003$) in the selenium group. In addition, within-group differences indicated a significant decrease in GPx ($P=0.001$) and a significant increase in serum triglycerides ($P=0.04$), VLDL-cholesterol ($P=0.04$), and creatinine ($P=0.006$) in the placebo group.

Baseline levels of triglycerides, VLDL-cholesterol, and total-/HDL-cholesterol ratio were significantly different between the two groups. Therefore, we adjusted the analyses for baseline values of these biochemical parameters, age, and BMI (Data not shown). After this adjustment, no significant changes in our findings occurred except for serum triglycerides ($P=0.04$), VLDL- ($P=0.04$), and HDL-cholesterol levels ($P=0.03$).

Discussion

In this clinical trial, we assessed the effects of selenium intake on glycemic control and lipid profiles among patients with DN. We found that selenium administration for 12 weeks among patients with DN had beneficial effects on plasma GPx, serum insulin levels, HOMA-IR, and HOMA-B, but it did not affect FPG, QUICKI, and lipid profiles. To our knowledge, the current randomized clinical trial is the first examining the effects of selenium intake on glycemic control and lipid concentrations in patients with DN.

Patients with DN are susceptible to insulin resistance and increased levels of lipid profiles [26]. The current study indicated that patients who received selenium supplements for 12 weeks had a significant decrease in serum insulin concentrations, HOMA-IR, and HOMA-B compared with the placebo. We have previously shown the beneficial effects of selenium supplementation on markers of insulin resistance with a dose of 200 μg/day for 6 months among patients with CIN1

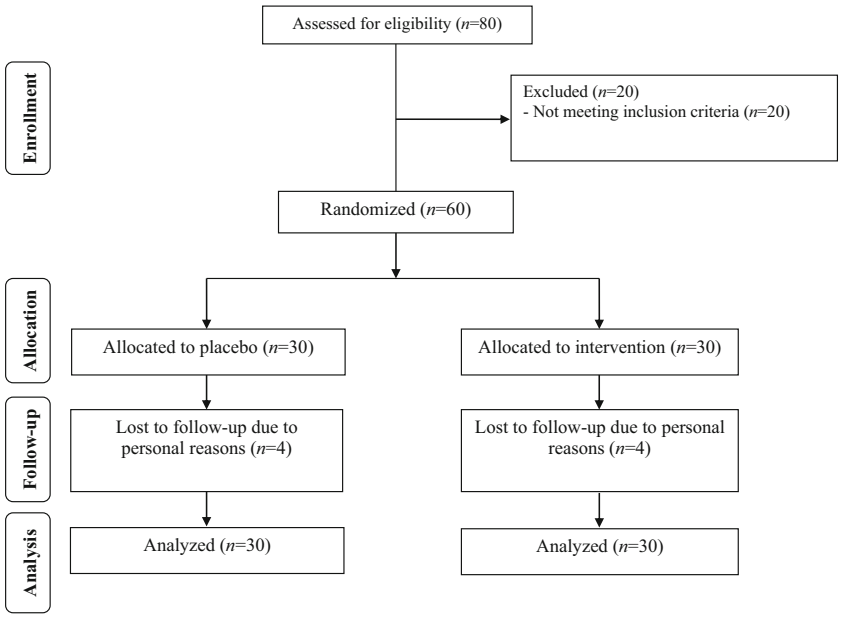

Fig. 1 Summary of patient flow diagram

Table 1 General characteristics of study participants[a]

	Placebo group ($n = 30$)	Selenium group ($n = 30$)	P[b]
Gender (%)			
Male	15 (50.0)	15 (50.0)	1.00†
Female	15 (50.0)	15 (50.0)	
Type of diabetes (%)			
Type 1	3 (10.0)	3 (10.0)	1.00†
Type 2	27 (90.0)	27 (90.0)	
Duration of DM (year)	15.8 ± 2.8	16.2 ± 2.5	0.53
Age (y)	61.4 ± 9.3	63.1 ± 12.6	0.56
Height (cm)	160.1 ± 10.1	160.4 ± 9.0	0.18
Weight at study baseline (kg)	77.2 ± 10.1	79.5 ± 15.1	0.50
Weight at end-of-trial (kg)	77.3 ± 10.2	79.6 ± 15.0	0.51
Weight change (kg)	0.1 ± 0.4	0.1 ± 0.4	0.65
BMI at study baseline (kg/m^2)	30.4 ± 4.9	29.8 ± 5.8	0.69
BMI at end-of-trial (kg/m^2)	30.4 ± 4.9	29.8 ± 5.8	0.68
BMI change (kg/m^2)	0.03 ± 0.1	0.01 ± 0.2	0.62
Insulin therapy (%)	22 (73.3)	21 (70)	0.77†
Antidiabetic drugs (%)			
Metformin	3 (10.0)	3 (10.0)	
Metformin + gliclazide	15 (50.0)	13 (43.3)	0.86†
Metformin + gliclazide + repaglinide	12 (40.0)	14 (46.7)	
Antilipidemic drug (%)			
Statins	18 (75.0)	16 (66.7)	
Fibrates	2 (8.3)	3 (12.5)	0.80†
Statins and fibrates	4 (16.7)	5 (20.8)	

[a] Data are means ± SDs

[b] Obtained from independent t test

†Obtained from the Pearson Chi-square test

DM diabetes mellitus

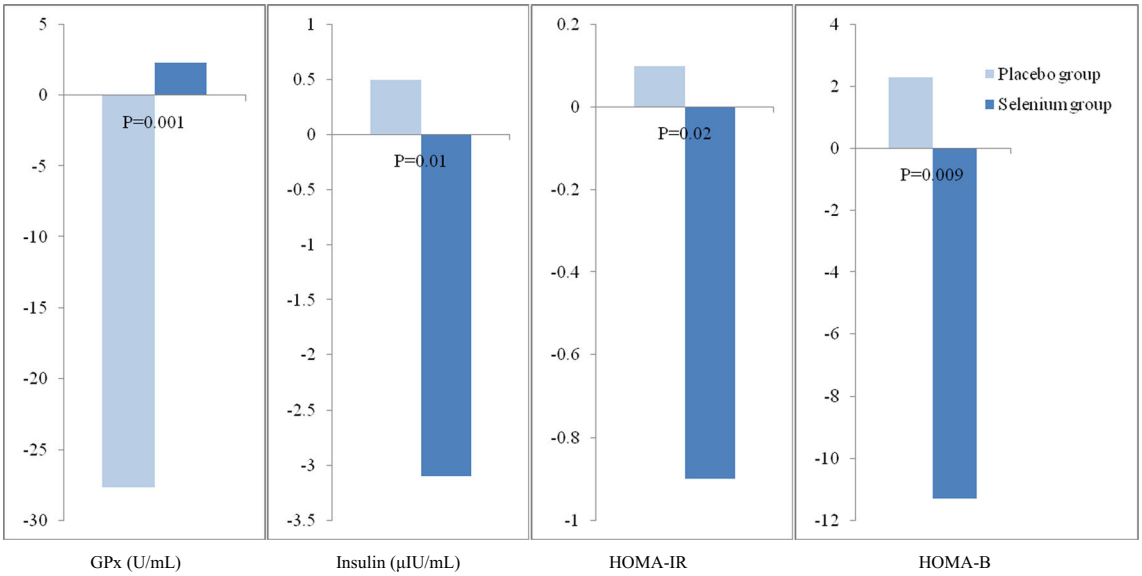

Fig. 2 Changes in (means ± standard deviation) of GPx and markers of insulin resistance after 12 weeks of intervention. *GPx*, glutathione peroxidase; *HOMA-IR*, homeostasis model of assessment-estimated insulin resistance; *HOMA-B*, homeostasis model of assessment-estimated β cell function

[13] and 200 μg/day for 8 weeks in patients with PCOS [15]. In another study by Alizadeh et al. [20], the use of 200 μg/day of selenium supplements for 6 weeks also led to decreased serum insulin concentrations and HOMA-IR among women with central obesity. In addition, oral selenate supplementation in diabetic *db/db* mice for 9 weeks resulted in a significant increase in plasma insulin levels [19]. Campbell et al. [27] showed that selenium stimulated pancreatic β cell gene expression and enhanced islet function in cell culture. Some investigators did not observe such beneficial effects of selenium supplementation on glucose homeostasis parameters. For instance, a 3-month supplementation with 200 μg/day of selenium among patients with T2DM did not influence circulating levels of insulin [21]. The discrepancies between our findings and those of previous reports might be explained by the dosage of selenium supplements used, the intervention time, the study participants, the quality of the supplements, their purity and bioavailability, as well as the time/period of administration. Impaired insulin metabolism appears to play a main role in kidney dysfunction by inducing glomerular hyperfiltration, endothelial dysfunction, and increased vascular permeability [28]. Previous studies have exhibited that intensive glycemic control in patients with T2DM decreased progression of DN and diabetic retinopathy [29]. Furthermore, few studies in patients with T2DM indicated that hyperglycemic control decreased expressions of inflammatory cytokines, such as monocyte chemoattractant protein-1, intercellular adhesion molecule-1, tumor necrosis factor-α (TNF-α), and interleukin 6 (IL-6) [30, 31]. Selenium intake may improve glycemic status through regulating the expression of genes responsible for synthesis of enzymes involved in the carbohydrate metabolism, increased glycogen levels as well as decrease in activity of glucose-6-phoshatse and glycogen phosphorylase [22] and the inhibition of inflammatory cytokines including TNF-α and IL-1 [32].

We found that selenium supplementation among patients with DN for 12 weeks did not affect lipid concentrations compared with the placebo. Overall, few studies have evaluated the impacts of selenium administration on lipid concentrations. In a Cochrane systematic review, Rees et al. [33] observed that selenium supplementation reduced total cholesterol but it did not reach statistical significance. We previously showed that taking 200 μg/day of selenium supplements for 8 weeks among PCOS women decreased serum levels of triglycerides and VLDL-cholesterol, without any impact on other lipid profiles [15]. With regard to the effect of selenium administration on lipid concentrations, few trials have assessed the effect of selenium intake in combination with other micronutrients on blood lipids. For instance, in a randomized trial by Zhang et al.[34] in a rural Chinese population with a low dietary intake of selenium, it was observed that long-term combined supplementation with selenium (37.5 μg), vitamin C, and vitamin E led to a small but significant rise in total- and LDL- cholesterol concentrations, although HDL-cholesterol concentrations were not affected. Impaired insulin function and T2DM are associated with a clustering of interrelated plasma lipid and lipoprotein abnormalities including reduced HDL-cholesterol and elevated triglyceride levels [35]. There is evidence that abnormalities in each of these lipid profiles is associated with increased risk of coronary artery disease (CAD), the leading cause of death in patients with T2DM [35]. Epidemiologic studies have reported that dyslipidemia in diabetes is associated with higher CAD risk and mortality [36, 37]. The absence of a significant effect on lipid profiles in the current study might be explained by the conditions of study participants,

Table 2 Metabolic profiles at study baseline and after 3 months intervention in patients with DN that received either selenium supplements or placebo[a]

	Placebo group ($n = 30$)				Selenium group ($n = 30$)				P^c		
	Baseline	End-of-trial	Change	P^b	Baseline	End-of-trial	Change	P^b	Time	Group	Time × Group
FPG (mg/dL)	122.4 ± 26.5	127.1 ± 50.6	4.7 ± 45.1	0.57	112.2 ± 44.0	112.9 ± 33.1	0.7 ± 40.7	0.92	0.63	0.16	0.71
QUICKI	0.30 ± 0.02	0.30 ± 0.02	0.0003 ± 0.01	0.42	0.31 ± 0.03	0.32 ± 0.02	0.009 ± 0.01	0.003	0.005	0.02	0.08
Triglycerides (mg/dL)	176.5 ± 87.8	194.7 ± 87.4	18.2 ± 48.0	0.04	130.1 ± 51.2	134.1 ± 47.2	4.0 ± 27.4	0.43	0.03	0.004	0.16
VLDL-cholesterol (mg/dL)	35.3 ± 17.5	39.0 ± 17.5	3.7 ± 9.6	0.04	26.0 ± 10.2	26.8 ± 9.4	0.8 ± 5.5	0.43	0.03	0.004	0.16
Total cholesterol (mg/dL)	163.8 ± 33.0	162.3 ± 36.8	−1.5 ± 15.1	0.59	149.7 ± 32.7	154.5 ± 32.5	4.8 ± 20.0	0.19	0.47	0.19	0.17
LDL-cholesterol (mg/dL)	83.3 ± 26.8	79.9 ± 30.2	−3.4 ± 12.9	0.16	76.9 ± 22.8	80.5 ± 23.2	3.6 ± 15.4	0.20	0.95	0.65	0.06
HDL-cholesterol (mg/dL)	45.2 ± 8.3	43.4 ± 7.6	−1.8 ± 5.5	0.09	46.8 ± 7.8	47.2 ± 9.3	0.4 ± 4.1	0.59	0.28	0.20	0.09
Total-/HDL-cholesterol ratio	3.7 ± 0.7	3.8 ± 0.7	0.1 ± 0.4	0.32	3.2 ± 0.6	3.3 ± 0.6	0.1 ± 0.4	0.23	0.12	0.01	0.93
Creatinine (mg/dL)	1.5 ± 0.8	1.6 ± 0.8	0.1 ± 0.2	0.006	1.4 ± 0.8	1.5 ± 0.8	0.1 ± 0.2	0.41	0.009	0.71	0.11
BUN (mg/dL)	26.7 ± 17.9	26.7 ± 18.8	0.05 ± 8.9	0.97	20.9 ± 10.9	18.3 ± 8.9	−2.6 ± 5.8	0.03	0.21	0.07	0.20

[a] Data are means ± SDs

[b] Obtained from paired-samples *t* tests

[c] Obtained from repeated measures ANOVA test

BUN blood urea nitrogen, *DN* diabetic nephropathy, *FPG* fasting plasma glucose, *QUICKI* quantitative insulin sensitivity check index

dosages of selenium supplements as well as the baseline levels of lipid profiles in study participants.

Our study had some limitations. Due to the budget limitation, we did not evaluate the effects of selenium administration on plasma or urine selenium and HbA1C. It must be kept in mind that the biomarkers we measured in the current study are all routine analyses and no significant molecular analyses were done in this study due to limited funding for research projects in developing countries. Therefore, performance of molecular analyses including measurement of malondialdehyde, superoxide dismutase, and glutathione are warranted in future studies. In addition, we could not assess the effects of selenium administration of other selenium-dependent antioxidant enzymes including thioredoxin reductase and the signaling pathway involved in DN. The GPx and other antioxidant/oxidant analyses should have been performed in erythrocytes instead of plasma, because oxidation occurs in lipids, protein, and nucleic acids. However, due to some limitations we couldn't perform these analyses. Therefore, our findings should be interpreted with caution. The high standard deviations (SDs) of dependent variables in some cases such as triglycerides and LDL-cholesterol might make the interpretation of our findings difficult. Such high SDs might be explained by the small number of participants in the study, which was a limitation.

Taken together, our study indicated that selenium supplementation for 12 weeks among patients with DN had beneficial effects on plasma GPx, serum insulin levels, HOMA-IR, and HOMA-B; however, it did not affect FPG, QUICKI, and lipid profiles.

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Authors' Contributions ZA contributed in conception, data collection, and manuscript drafting. FB, MK, AS, and AE contributed in conception, data collection, and manuscript drafting. All authors read and approved the final version of the paper.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no competing interests.

Guarantor ZA is the guarantor of this work.

Clinical Registration http://www.irct.ir.IRCT2015060622562N1

References

1. Muchova J, Orszaghova Z, Zitnanova I, Trebaticky B, Breza J, Durackova Z (2014) The effect of natural polyphenols on the oxidative stress markers in patients with diabetic nephropathy. Free Radic Biol Med 75(Suppl 1):S42. doi:10.1016/j.freeradbiomed.2014.10.795

2. Filippone EJ, Gupta A, Farber JL (2014) Normoglycemic diabetic nephropathy: the role of insulin resistance. Case Rep Nephrol Urol 4:137–143
3. Genuth S (2006) Insights from the diabetes control and complications trial/epidemiology of diabetes interventions and complications study on the use of intensive glycemic treatment to reduce the risk of complications of type 1 diabetes. Endocr Pract 12(Suppl 1):34–41
4. Bjornstad P, Maahs DM, Cherney DZ et al (2014) Insulin sensitivity is an important determinant of renal health in adolescents with type 2 diabetes. Diabetes Care 37:3033–3039
5. Sedighi O, Makhlough A, Shokrzadeh M, Hoorshad S (2014) Association between plasma selenium and glutathione peroxidase levels and severity of diabetic nephropathy in patients with type two diabetes mellitus. Nephrourol Mon 6, e21355. doi:10.5812/numonthly.21355, eCollection 2014
6. Kornhauser C, Garcia-Ramirez JR, Wrobel K, Perez-Luque EL, Garay-Sevilla ME (2008) Serum selenium and glutathione peroxidase concentrations in type 2 diabetes mellitus patients. Prim Care Diabetes 2:81–85
7. Darmaun D, Smith SD, Sweeten S, Sager BK, Welch S, Mauras N (2005) Evidence for accelerated rates of glutathione utilization and glutathione depletion in adolescents with poorly controlled type 1 diabetes. Diabetes 54:190–196
8. Hu Y, McIntosh GH, Young GP (2012) Selenium-rich foods: a promising approach to colorectal cancer prevention. Curr Pharm Biotechnol 13:165–172
9. Kalkan Ucar S, Coker M, Sozmen E, Goksen Simsek D, Darcan S (2010) An association among iron, copper, zinc, and selenium, and antioxidative status in dyslipidemic pediatric patients with glycogen storage disease types IA and III. J Trace Elem Med Biol 24:42–45
10. Naziroglu M, Yoldas N, Uzgur EN, Kayan M (2013) Role of contrast media on oxidative stress, Ca(2+) signaling and apoptosis in kidney. J Membr Biol 246:91–100
11. Naziroglu M, Guler M, Ozgul C, Saydam G, Kucukayaz M, Sozbir E (2014) Apple cider vinegar modulates serum lipid profile, erythrocyte, kidney, and liver membrane oxidative stress in ovariectomized mice fed high cholesterol. J Membr Biol 247:667–673
12. Rayman MP (2012) Selenium and human health. Lancet 379:1256–1268
13. Karamali M, Nourgostar S, Zamani A, Vahedpoor Z, Asemi Z (2015) The favourable effects of long-term selenium supplementation on regression of cervical tissues and metabolic profiles of patients with cervical intraepithelial neoplasia: a randomised, double-blind, placebo-controlled trial. Br J Nutr 114:2039–2045
14. Asemi Z, Jamilian M, Mesdaghinia E, Esmaillzadeh A (2015) Effects of selenium supplementation on glucose homeostasis, inflammation, and oxidative stress in gestational diabetes: Randomized, double-blind, placebo-controlled trial. Nutrition 31:1235–1242
15. Jamilian M, Razavi M, Fakhrie Kashan Z, Ghandi Y, Bagherian T, Asemi Z (2015) Metabolic response to selenium supplementation in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Clin Endocrinol 82:885–891
16. Kose SA, Naziroglu M (2015) N-acetyl cysteine reduces oxidative toxicity, apoptosis, and calcium entry through TRPV1 channels in the neutrophils of patients with polycystic ovary syndrome. Free Radic Res 49:338–346
17. Kose SA, Naziroglu M (2014) Selenium reduces oxidative stress and calcium entry through TRPV1 channels in the neutrophils of patients with polycystic ovary syndrome. Biol Trace Elem Res 158:136–142
18. Dhanya BL, Swathy RP, Indira M (2014) Selenium downregulates oxidative stress-induced activation of leukotriene pathway in experimental rats with diabetic cardiac hypertrophy. Biol Trace Elem Res 161:107–115
19. Wang C, Yang S, Zhang N et al (2014) Long-term supranutritional supplementation with selenate decreases hyperglycemia and promotes fatty liver degeneration by inducing hyperinsulinemia in diabetic db/db mice. PLoS One 9, e101315. doi:10.1371/journal.pone.0101315, eCollection 2014
20. Alizadeh M, Safaeiyan A, Ostadrahimi A et al (2012) Effect of L-arginine and selenium added to a hypocaloric diet enriched with legumes on cardiovascular disease risk factors in women with central obesity: a randomized, double-blind, placebo-controlled trial. Ann Nutr Metab 60:157–168
21. Faghihi T, Radfar M, Barmal M et al (2014) A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: effects on glucose homeostasis, oxidative stress, and lipid profile. Am J Ther 21:491–495
22. Chen H, Qiu Q, Zou C, Dou L, Liang J (2015) Regulation of hepatic carbohydrate metabolism by selenium during diabetes. Chem Biol Interact 232:1–6
23. Fasano E, Serini S, Mondella N et al (2014) Antioxidant and anti-inflammatory effects of selected natural compounds contained in a dietary supplement on two human immortalized keratinocyte lines. Biomed Res Int 2014:327452. doi:10.1155/2014/327452
24. Panduru NM, Saraheimo M, Forsblom C et al (2015) Urinary adiponectin is an independent predictor of progression to end-stage renal disease in patients with type 1 diabetes and diabetic nephropathy. Diabetes Care 38:883–890
25. Pisprasert V, Ingram KH, Lopez-Davila MF, Munoz AJ, Garvey WT (2013) Limitations in the use of indices using glucose and insulin levels to predict insulin sensitivity: impact of race and gender and superiority of the indices derived from oral glucose tolerance test in African Americans. Diabetes Care 36:845–853
26. Joven MH, Anderson RJ (2015) Update on blood pressure control and renal outcomes in diabetes mellitus. Curr Diab Rep 15:44. doi:10.1007/s11892-015-0613-6
27. Campbell SC, Aldibbiat A, Marriott CE et al (2008) Selenium stimulates pancreatic beta-cell gene expression and enhances islet function. FEBS Lett 582:2333–2337
28. De Cosmo S, Menzaghi C, Prudente S, Trischitta V (2013) Role of insulin resistance in kidney dysfunction: insights into the mechanism and epidemiological evidence. Nephrol Dial Transplant 28:29–36
29. Mima A (2013) Inflammation and oxidative stress in diabetic nephropathy: new insights on its inhibition as new therapeutic targets. J Diabetes Res 2013:248563
30. Antoniades C, Tousoulis D, Marinou K et al (2007) Effects of insulin dependence on inflammatory process, thrombotic mechanisms and endothelial function, in patients with type 2 diabetes mellitus and coronary atherosclerosis. Clin Cardiol 30:295–300
31. Ye SD, Zheng M, Zhao LL et al (2009) Intensive insulin therapy decreases urinary MCP-1 and ICAM-1 excretions in incipient diabetic nephropathy. Eur J Clin Investig 39:980–985
32. Brigelius-Flohe R, Banning A, Kny M, Bol GF (2004) Redox events in interleukin-1 signaling. Arch Biochem Biophys 423:66–73
33. Rees K, Hartley L, Day C, Flowers N, Clarke A, Stranges S (2013) Selenium supplementation for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 1, CD009671. doi:10.1002/14651858.CD009671.pub2
34. Zhang L, Gail MH, Wang YQ et al (2006) A randomized factorial study of the effects of long-term garlic and micronutrient

supplementation and of 2-wk antibiotic treatment for helicobacter pylori infection on serum cholesterol and lipoproteins. Am J Clin Nutr 84:912–919
35. Krauss RM (2004) Lipids and lipoproteins in patients with type 2 diabetes. Diabetes Care 27:1496–1504
36. Tseng CH, Tseng CP, Chong CK, Cheng JC, Tai TY (2006) Independent association between triglycerides and coronary artery disease in Taiwanese type 2 diabetic patients. Int J Cardiol 111:80–85
37. Bos G, Dekker JM, Nijpels G et al (2003) A combination of high concentrations of serum triglyceride and non-high-density-lipoprotein-cholesterol is a risk factor for cardiovascular disease in subjects with abnormal glucose metabolism–the Hoorn study. Diabetologia 46:910–916