Selenium Supplementation Affects Insulin Resistance and Serum hs-CRP in Patients with Type 2 Diabetes and Coronary Heart Disease

Authors
A. Farrokhian[1], F. Bahmani[2], M. Taghizadeh[2], S. M. Mirhashemi[2], M. H. Aarabi[2], F. Raygan[1], E. Aghadavod[2], Z. Asemi[2]

Affiliations
[1] Department of Cardiology, School of Medicine, Kashan University of Medical Sciences, Kashan, I. R. Iran
[2] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I. R. Iran

Key words
- selenium supplementation
- type 2 diabetes mellitus
- coronary heart disease
- insulin resistance

Abstract

To our knowledge, this study is the first indicating the effects of selenium supplementation on metabolic status of patients with type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD). This study was conducted to evaluate the effects of selenium supplementation on metabolic profiles, biomarkers of inflammation, and oxidative stress of patients with T2DM and CHD. This randomized, double-blind, placebo-controlled trial was performed among 60 patients with T2DM and CHD aged 40–85 years. Participants were randomly divided into 2 groups. Group A received 200 µg selenium supplements (n=30) and group B received placebo per day (n=30) for 8 weeks. Fasting blood samples were taken at the beginning of the study and after 8-week intervention to quantify metabolic profiles. After 8 weeks, compared with the placebo, selenium supplementation resulted in a significant decrease in serum insulin levels (−2.2±4.6 vs. +3.6±8.4 µIU/ml, p=0.001), homeostasis model of assessment-insulin resistance (HOMA-IR) (−0.7±1.3 vs. +0.9±2.4, p=0.004), homeostatic model assessment-beta cell function (HOMA-B) (−7.5±17.2 vs. +15.1±34.5, p=0.002) and a significant increase in quantitative insulin sensitivity check index (QUICKI) (+0.01±0.03 vs. −0.01±0.03, p=0.02). In addition, patients who received selenium supplements had a significant reduction in serum high-sensitivity C-reactive protein (hs-CRP) (−1372.3±2318.8 vs. −99.8±1453.6 ng/ml, p=0.01) and a significant rise in plasma total antioxidant capacity (TAC) concentrations (+301.3±400.6 vs. −127.2±428.0 mmol/l, p<0.001) compared with the placebo. A 200 µg/day selenium supplementation among patients with T2DM and CHD resulted in a significant decrease in insulin, HOMA-IR, HOMA-B, serum hs-CRP, and a significant increase in QUICKI score and TAC concentrations.

Supporting Information for this article is available online at http://www.thieme-connect.de/products

received 15.07.2015
accepted 11.11.2015

Bibliography
DOI http://dx.doi.org/10.1055/s-0035-1569276
Published online: Janury 7, 2016
Horm Metab Res 2016; 48: 263–268

ISSN 0018-5043

Correspondence
Z. Asemi, Ph.D.
Department of Nutrition
Kashan University of Medical Sciences
Iran
Tel.: +98/31/55463 378
Fax: +98/31/55463 377
asemi_r@yahoo.com

Abbreviations

CHD	Coronary heart disease
FPG	Fasting plasma glucose
GSH	Glutathione
HOMA-IR	Homeostasis model of assessment-estimated insulin resistance
HOMA-B	Homeostasis model of assessment-estimated b cell function
hs-CRP	High-sensitivity C-reactive protein
MDA	Malondialdehyde
NO	Nitric oxide
QUICKI	Quantitative insulin sensitivity check index
TAC	Total antioxidant capacity
T2DM	Type 2 diabetes mellitus

Introduction

Coronary heart disease (CHD) is a main cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) [1]. In patients with T2DM, there is an increased risk of poor prognosis after cardiovascular (CV) events and a higher risk of mortality at similar levels of coronary artery disease compared with patients without diabetes [2,3]. Hyperglycemia and impaired insulin metabolism are the main players in the development of atherosclerosis and its abnormalities [4]. Elevated circulating levels of triglycerides and VLDL-cholesterol in T2DM may contribute to the development of metabolic complications of obesity, including nonalcoholic fatty liver disease, cardiovascular dysfunction, and stroke [5]. In addition, previous studies have reported that metabolic abnormalities results in

overproduction of free radicals and reactive oxygen species (ROS), which in turn play an important role in precipitating diabetic vascular disease [6–8].

Various nutritional factors such as magnesium, folic acid, vitamins B_{12} and B_6, and polyunsaturated fatty acids (PUFAs) appear to be significantly beneficial for patients with T2DM and CHD [9,10]. There is scarce information on the beneficial effects of selenium supplementation on metabolic status in patients with T2DM and CHD and the results are inconsistent. Few prospective studies suggest that circulating levels of low selenium is a risk factor for cardiovascular disease [11,12]. However, a randomized clinical trial showed no effect of selenium supplementation (200 µg daily) during 7.6 years of follow-up on the primary prevention of cardiovascular disease [13]. Current data support the beneficial effect of selenium in carbohydrate, fat metabolism and inflammation, and oxidative stress. In a study, Valenta et al. [14] observed that high-dose selenium supplementation for 14 days (1000 µg on day 1 and 500 µg/day on days 2–14) significantly decreased C-reactive protein (CRP) levels in patients with systemic inflammatory response syndrome (SIRS)/sepsis. In addition, our previous study among patients with polycystic ovary syndrome (PCOS) had demonstrated that 200 µg/day selenium supplementation for 8 weeks had beneficial effects on insulin metabolism parameters, triglycerides, and VLDL-cholesterol concentrations, while it did not affect fasting plasma glucose (FPG) and other lipid concentrations [15]. However, no significant change in high-sensitivity C-reactive protein (hs-CRP) concentrations was seen among centrally obese women who received 200 µg selenium supplements for 6 weeks [16].

Selenium intake may reduce insulin resistance through inhibiting the expression of cyclooxygenase (COX)-2 and P-selectin [17]. Beneficial effects of selenium supplementation on inflammatory factors may be mediated by inhibiting the activation of NF-kappa B by modulating selenoprotein genes expression [18]. Overall, limited data are available indicating the effects of selenium supplementation on metabolic status of patients with T2DM and CHD. Therefore, we hypothesized that selenium supplementation might affect metabolic profiles, biomarkers of inflammation, and oxidative stress among patients with T2DM and CHD. The aim of this study was to examine the effects of selenium supplementation on metabolic status among patients with T2DM and CHD.

Subjects and Methods

Participants

The study population consisted of patients with T2DM and CHD recruited from the medical outpatient clinic affiliated to Kashan University of Medical Sciences (KUMS), Kashan, Iran between July–September 2014. In the present study, for estimating the sample size, we used a randomized clinical trial sample size formula where type one (α) and type 2 (β) error were 0.05 and 0.20 (power = 80 %), respectively. According to a previous trial [16], we used 0.40 as SD and 0.30 as the change in mean (d) of the homeostasis model of assessment-insulin resistance (HOMA-IR) as main variable. Based on this, we needed 25 subjects in each group. In the current study, we used HOMA-IR variable to estimate sample size because the largest sample size was obtained when this variable was used. Therefore, the sample size obtained based on this variable covered the required sample size for all other variables. Considering 5 dropouts in each group, the final sample size was determined to be 30 patients in each group. T2DM patients aged 40–85 years and with stable CHD were included in the current study. Diagnosis of T2DM was performed according to the criteria of American Diabetes Association [19]: patients who have one of the following criteria were considered as T2DM: FPG ≥ 126 mg/dl, blood sugar (BS) 2-h pp ≥ 200 mg/dl, and HbA1c ≥ 6.5 %. In addition, patients who have one or more of the following criteria was considered as stable CHD: record of myocardial infarction, document of at least 50 % stenosis in one or more coronary vessels upon cardiac catheterization evaluated by angiography, document of exercise-induced ischemia by treadmill electrocardiogram or nuclear perfusion stress imaging, and a history of coronary revascularization [19]. Patients with one of the following conditions were excluded in the present study: smokers, intake of selenium or antioxidant supplements within the last 3 months, an acute myocardial infarction within the past 3 months, cardiac surgery within the past 3 months, and significant renal failure or liver failure. All procedures were done according to the ethical standards of the responsible committee and the Helsinki Declaration. The ethical committee of KUMS confirmed the trial and informed consent was obtained from all patients. The trial was registered in the Iranian website (www.irct.ir) for registration of clinical trials (IRCT code: IRCT201407015623N22).

Study design

At the beginning of the study and after stratification for pre-intervention BMI (< 25 and ≥ 25 kg/m^2) and age (< 60 and ≥ 60 y), patients with T2DM and CHD were divided into 2 groups randomly. Group A received 200 µg daily selenium supplements as tablet (20 females and 10 males: n = 30) and group B placebo (20 females and 10 males: n = 30) daily for 8 weeks after dinner for the same period. Due to the lack of evidence about the appropriate dosage of selenium and the duration of intervention for patients with T2DM and CHD, we used the above-mentioned dose of selenium and the duration of intervention based on a previous study in patients with PCOS [20]. As the prevalence of metabolic syndrome (MetS) including T2DM and CHD is more common in the age of higher than 40 years, we selected 40–85 years old in the current study. Selenium supplements and its placebos (cellulose) were provided by Nature Made Pharmaceutical Company (California, USA) and Barij Essence Pharmaceutical Company (Kashan, Iran), respectively. Furthermore, selenium supplements and placebos were in the same form of package and the patients and researcher were not aware of the content of the pack until the end-of-intervention. Random assignment was done by the use of computer-generated random numbers. Randomization and allocation were hidden from the researcher and patients until the main analyses were completed. A trained nutritionist at cardiology clinic did the randomized allocation sequence, enrolled patients, and assigned patients to interventions. At the beginning of the study, patients were requested to preserve their regular diet and levels of physical activity throughout the trial period. The use of selenium supplements and placebos throughout the study was checked through by asking participants to bring the medication containers. To increase the compliance, all patients received short messages on their cell phones to take the supplements each day. All participants provided 3 dietary records (2 week days and 1 week end) and 3 physical activity records to make sure that they maintained their usual diet and physical activity during intervention. Both dietary and physical activity records were obtained at week 2, 4,

and 6 of intervention. Physical activity was described as metabolic equivalents (METs) in hours per day. To calculate the METs for each patients, we multiplied the times (in hour per day) reported for each physical activity by its related METs coefficient by standard tables [21]. Dietary intakes of participants at mentioned weeks were assessed by means of 3-day dietary records. To obtain nutrient intakes of patients according to 3-day food record, Nutritionist IV software (First Databank, San Bruno, CA) adjusted for Iranian food pattern was used.

Assessment of anthropometric measures

Weight (Seca, Hamburg, Germany) was determined at the beginning of the study and after 8-week intervention in cardiology clinic by a trained nutritionist. Body weight was assayed without shoes in a minimal clothing condition by the use of a digital scale to the nearest 0.1 kg. Height (Seca, Hamburg, Germany) was determined by a nonstretched tape measure to the nearest 0.1 cm. BMI was determined as weight in kg divided by height in meters squared.

Outcomes

As markers of insulin metabolism and CRP are the most important variable in patients with T2DM and CHD, we considered markers of insulin metabolism and hs-CRP as primary outcomes in the current study. Secondary outcomes were lipid profiles, nitric oxide (NO), and biomarkers of oxidative stress. Fasting blood samples (10 mL) were collected at the beginning of the study and 8 weeks after the intervention at Kashan reference laboratory in an early morning after an overnight fast. Blood samples were immediately centrifuged (Hettich, Tuttlingen, Germany) at 3 500 rpm for 10 min to separate serum. FPG and serum lipid profiles were also quantified on the day of blood collection. The samples were then stored at −80 °C before final analysis at the KUMS reference laboratory. Serum insulin concentrations were assayed by ELISA (Monobind, California, USA). The intra- and inter-assay CVs for serum insulin were 3.0 and 5.4 %, respectively. HOMA-IR, β-cell function (HOMA-B), and the quantitative insulin sensitivity check index (QUICKI) were determined according to suggested formulas [22]. Commercial kits were used to measure FPG, serum triglycerides, VLDL-, total-, LDL-, and HDL-cholesterol concentrations (Pars Azmun, Tehran, Iran). All inter- and intra-assay CVs for FPG and lipid profiles measurements were less than 5 %. Serum hs-CRP concentrations were determined by ELISA kit (LDN, Nordhorn, Germany) with intra- and inter-assay CVs of 2.5 and 4.6 %, respectively. The plasma NO concentrations were determined using the Giess method modified by Tatsh et al. [23]. Plasma TAC concentrations were determined by the use of ferric reducing antioxidant power (FRAP) developed by Benzie and Strain [24], total glutathione (GSH) by the method of Beutler et al. [25], and malondialdehyde (MDA) concentrations by the thiobarbituric acid reactive substances (TBARs) spectrophotometric test [26].

Statistical methods

In the current study, we used Kolmogrov-Smirnov test to determine the normal distribution of variables. The intention-to-treat (ITT) analysis of the primary study end-point was done for all the randomly allocated participants. Missing data from dropped out participants were imputed using the method of "Last Observation Carried Forward (LOCF)". To detect differences in general characteristics, macro- and micronutrient intakes between the 2 groups, independent samples Student's *t*-test was used. Pearson Chi-square test was used for comparison of categorical variables. To identify within-group differences (baseline and end-of-trial), paired-samples *t*-tests was used. To determine the effects of selenium supplementation on markers of insulin metabolism, lipid concentrations, biomarkers of inflammation and oxidative stress, we used 2-factor repeated measures ANOVA, where treatment by time interactions were tested by using Pillai's trace. To evaluate if the magnitude of the change in dependent variables depended on baseline values, age and baseline BMI, we adjusted all analyses for baseline values, age and baseline BMI to avoid potential bias. These analyses were also done using 2-factor repeated measures ANOVA. A p-value of <0.05 was considered statistically significant. All statistical analyses were done using the Statistical Package for Social Science version 17 (SPSS Inc., Chicago, IL, USA).

Results

At the screening visit, 550 persons were screened. A total of 490 subjects among the 550 screened persons were excluded from the first visit (**Suppl. Fig. S1**). In the present study, among patients in the selenium group, 3 persons [withdrawn due to personal reasons (n = 3)] and in the placebo group, 3 individuals [withdrawn due to personal reasons (n = 3)] did not complete the trial. Finally, 54 participants [selenium (n = 27) and placebo (n = 27)] completed the trial. However, as the analysis was based on ITT principle, all 60 patients (30 in each group) were included in the final analysis. On average, the rate of compliance in our study was high, such that higher than 90 % of tablets were taken throughout the study in both groups. No side effects were reported after selenium supplementation in patients with T2DM and CHD throughout the study.

Mean age and height of study participants were not statistically different between selenium and placebo groups. Baseline weight, BMI, and METs as well as their means before and after 8-week intervention were not significantly different comparing the 2 groups (**Suppl. Table S1**).

Based on the 3-day dietary records obtained throughout the intervention, no significant difference was observed between the 2 groups in terms of dietary intakes of energy, carbohydrates, proteins, fats, saturated fatty acids (SFAs), polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs), cholesterol, total dietary fiber (TDF), selenium, magnesium, manganese, and zinc (**Suppl. Table S2**).

After 8 weeks, compared with the placebo, selenium supplementation resulted in a significant decrease in serum insulin levels (−2.2 ± 4.6 vs. +3.6 ± 8.4 μIU/ml, p = 0.001), HOMA-IR (−0.7 ± 1.3 vs. +0.9 ± 2.4, p = 0.004), HOMA-B (−7.5 ± 17.2 vs. +15.1 ± 34.5, p = 0.002) and a significant increase in QUICKI (+0.01 ± 0.03 vs. −0.01 ± 0.03, p = 0.02) (**Table 1**). In addition, patients who received selenium supplements had a significant reduction in serum hs-CRP (−1 372.3 ± 2 318.8 vs. −99.8 ± 1 453.6 ng/ml, p = 0.01) and a significant rise in plasma TAC concentrations (+301.3 ± 400.6 vs. −127.2 ± 428.0 mmol/l, $p<0.001$) compared with the placebo. Our findings revealed no significant changes in FPG, lipid concentrations, plasma NO, GSH, and MDA. Within-group changes demonstrated significant reductions in serum insulin concentrations (p = 0.01), HOMA-IR (p = 0.009), HOMA-B (p = 0.02), hs-CRP (p = 0.003), NO (p = 0.007) and a significant rise in plasma TAC concentrations ($p<0.001$) in the selenium group. In addition, within-group changes revealed a significant increase in

Table 1 Metabolic profiles, inflammatory factors, and biomarkers of oxidative stress at baseline study and 8 weeks after the intervention in patients with T2DM and CHD.

	Placebo group (n = 30)			Selenium group (n = 30)			
	Wk0	Wk8	Change	Wk0	Wk8	Change	p-Value[a]
FPG (mg/dl)	133.9 ± 48.5	126.6 ± 52.5	−7.3 ± 35.3	124.2 ± 61.5	122.0 ± 66.0	−2.2 ± 58.5	0.69
Insulin (μIU/ml)	11.8 ± 7.3	15.4 ± 10.0 *	3.6 ± 8.4	13.5 ± 6.9	11.3 ± 5.6 *	−2.2 ± 4.6	0.001
HOMA-IR	3.9 ± 3.0	4.8 ± 3.5	0.9 ± 2.4	3.9 ± 2.6	3.2 ± 2.1 *	−0.7 ± 1.3	0.004
HOMA-B	31.3 ± 22.4	46.4 ± 42.2 *	15.1 ± 34.5	44.7 ± 35.7	37.2 ± 29.8 *	−7.5 ± 17.2	0.002
QUICKI	0.32 ± 0.03	0.31 ± 0.04	−0.01 ± 0.03	0.32 ± 0.02	0.33 ± 0.02	0.01 ± 0.03	0.02
Triglycerides (mg/dl)	150.3 ± 73.7	144.9 ± 68.7	−5.4 ± 46.9	163.0 ± 57.0	154.9 ± 57.4	−8.1 ± 41.6	0.81
VLDL-cholesterol (mg/dl)	30.1 ± 14.7	29.0 ± 13.7	−1.1 ± 9.4	32.6 ± 11.4	31.0 ± 11.5	−1.6 ± 8.3	0.81
Total cholesterol (mg/dl)	151.5 ± 28.6	149.7 ± 31.1	−1.8 ± 20.7	163.1 ± 29.8	159.2 ± 37.0	−3.9 ± 26.1	0.73
LDL-cholesterol (mg/dl)	73.7 ± 24.0	71.7 ± 23.4	−2.0 ± 20.6	80.9 ± 27.6	77.3 ± 31.2	−3.6 ± 22.1	0.76
HDL-cholesterol (mg/dl)	47.8 ± 7.5	49.0 ± 8.6	1.2 ± 6.0	49.7 ± 8.8	51.0 ± 11.0	1.3 ± 7.7	0.95
hs-CRP (ng/ml)	2676.5 ± 2684.9	2576.7 ± 2489.8	−99.8 ± 1453.6	3149.7 ± 3213.7	1777.4 ± 2041.3 *	−1372.3 ± 2318.8	0.01
NO (μmol/l)	37.1 ± 14.8	32.8 ± 12.9 *	−4.3 ± 9.3	46.0 ± 18.3	37.1 ± 17.1 *	−8.9 ± 16.7	0.19
TAC (mmol/l)	1156.5 ± 348.2	1029.3 ± 322.2	−127.2 ± 428.0	884.4 ± 327.2	1185.7 ± 278.8 *	301.3 ± 400.6	<0.001
GSH (μmol/l)	551.7 ± 162.6	530.0 ± 199.2	−21.7 ± 145.2	535.6 ± 132.6	505.2 ± 150.7	−30.4 ± 172.2	0.83
MDA (μmol/l)	5.3 ± 2.0	5.2 ± 2.0	−0.1 ± 1.2	5.2 ± 1.7	4.8 ± 1.9	−0.4 ± 1.5	0.42

All values are means ± SD. For abbreviations, see the abbreviation list

[a] p-Values represent the time by group interaction (computed by analysis of the 2-way repeated measures ANOVA)

* Differed significantly from the baseline

serum insulin (p = 0.02), HOMA-B (p = 0.02) and a significant reduction in NO concentrations (p = 0.01) in the placebo group. Baseline levels of NO were significantly different between the 2 groups. Therefore, we controlled the analyses for the baseline levels. However, after this adjustment no significant changes in our findings occurred. Additional adjustments for age and baseline BMI did not affect our findings (**Suppl. Table S3**).

Discussion

In this trial, which to the best of our knowledge is the first of its kind in patients with T2DM and CHD, we evaluated the effects of selenium supplementation on markers of insulin resistance, lipid profiles, biomarkers of inflammation, and oxidative stress. The major finding was that selenium supplementation improved insulin function, decreased serum hs-CRP, and increased plasma TAC concentrations in patients with T2DM and CHD. It must be kept in mind that results of randomized trials on selenium supplementation and the risk of T2DM are conflicting. In the large selenium and vitamin E Cancer Prevention Trial (SELECT), there was a small nonsignificant increase in the number of cases of adult-onset diabetes in subjects supplemented with 200 μg/day selenium [27] that diminished further on follow-up for an additional 18 months [5]. By contrast, the Nutritional Prevention of Cancer (NPC) trial revealed a significantly increased risk of T2DM in those supplemented with 200 μg/day selenium over an average period of 7.7 years [28]. Because a higher levels of selenium or higher intake increases the risk of T2DM and there is a growing pervasiveness of T2DM, it is imperative to evaluate the effect of selenium supplementation on the risk of T2DM. Interestingly, older adults with a relatively low selenium status did not show any diabetogenic effects after a 6-month supplementation with 100, 200, or 300 μg selenium/day [29]. Therefore, these findings suggest that selenium in excess may be the reason for the increased risk of T2DM found in those with a high selenium status and intake.

Our study revealed that patients who received selenium supplements for 8 weeks had a significant decrease in serum insulin concentrations, HOMA-IR, HOMA-B, and a significant rise in QUICKI compared with the placebo, but had no significant change in FPG and lipid concentrations. Few studies have evaluated the effects of selenium supplementation on markers of insulin metabolism and lipid concentrations. In our previous study, improved insulin function, triglycerides, and VLDL-cholesterol levels were seen following the administration of 200 μg/day selenium supplements for 8 weeks among PCOS women without no significant change in FPG and other lipid profiles [15]. In addition, taking 200 μg/day selenium supplements for 6 weeks led to a significant reduction in serum insulin concentrations and HOMA-IR among women with central obesity [16]. Furthermore, the administration of 100 μg selenium per day in pregnant women in the first trimester of pregnancy until delivery did not influence any significant change in lipid concentrations [30]. However, some studies did observe no significant effect of selenium supplementation on glucose homeostasis parameters. For example, 200 μg/day selenium supplementation among patients with T2DM for 3 months did not affect serum insulin concentrations as well as increased FPG concentrations [31]. Selenium intake may improve markers of insulin metabolism via its effect on inhibiting the expression of COX-2 and P-selectin [17] and inhibiting production of inflammatory cytokines including tumor necrosis factor-α (TNF- α) and IL-1 [32]. These suggest that selenium intake could alter the secretion profile of hepatocytes to one that favors the pro-inflammatory state associated with diabetes. However, there are animal [33, 34] and case control studies [35, 36] that indicate selenium may decrease insulin resistance. In addition, selenium has also been shown to have insulin-like properties [37], which in turn qualifies it as a potential antidiabetic agent. In addition, increased biomarkers of oxidative stress and inflammation play a major role in the etiology, pathogenesis, and complications of T2DM [38]. Experimental data suggest that supplementation with antioxidants including selenium could delay the development of T2DM by decreasing oxidative stress [39]. The absence of significant effect on lipid profiles in this study after the intake of selenium supplements might result from the distinct study designs, discrepancy in study participants, different dosages of selenium supplements as well as duration of the trial.

The present study has demonstrated that selenium supplementation in patients with T2DM and CHD resulted in a significant decrease in serum hs-CRP, but did not affect plasma NO concentrations compared with the placebo. In line with our findings, supplementation with daily one selenplus capsule containing 50 µg selenium, 8 mg zinc, 400 µg vitamin A, 125 mg vitamin C, and 40 mg vitamin E among rheumatoid arthritis patients [40] and 200 µg selenium among PCOS women [41] resulted in a significant decrease in hs-CRP concentrations among rheumatoid arthritis patients for 12 weeks. Similar relationships between plasma selenium and CRP concentration have also been reported previously in septic patients [42]. In another study, Scheurig et al. [43] reported that intake of dietary supplements containing vitamins E, C, B_1, B_2, B_3, B_5, B_6, B_9, B_{12}, and selenium was associated with decreased levels of CRP. Furthermore, a 4-week supplementation with dietary supplements containing 76 µg/day selenium, 9 mg/day beta-carotene, 1 500 mg/day vitamin C, 130 mg/day vitamin E, 45 mg/day zinc, and 150 mg/day garlic did not influence NO levels in allergic adults [44]. However, few researchers did not find such favorable effects of selenium supplementation on hs-CRP concentrations. For instance, administration of cereal biscuit with selenized onion, curcuma, and green tea among healthy adults for 2 months did not influence hs-CRP concentrations [45]. The beneficial effects of selenium supplementation on CRP concentrations may be explained by inhibiting the activation of nuclear factor kappa-B (NF-kappaB) [18] and increasing selenoprotein biosynthesis [46].

The present study indicates that selenium supplementation for 8 weeks among patients with T2DM and CHD increased plasma TAC, while did not affect plasma GSH and MDA concentrations compared with the placebo. In agreement with our study, erythrocyte antioxidant markers including TAC, glutathione peroxidase (GPX), superoxide dismutase (SOD), and catalase concentrations had significantly increased during 12 weeks supplementation selenplus capsule contained 50 µg selenium, 8 mg zinc, 400 µg vitamin A, 125 mg vitamin C, and 40 mg vitamin E [40]. In addition, a 2-month intervention with selenium and vitamin E supplementation reduced oxidative stress and enhanced total antioxidant status (TAS) in patients with pulmonary tuberculosis (TB) [47]. However, supplementation with 200 µg/day selenium for 3 weeks did not affect biomarkers of oxidative stress including TAS and GSH levels among overweight adults [48]. The favorable effects of selenium supplementation on biomarkers of oxidative stress may be mediated by participation in the erythrocyte glutathione (GSH)-Px system [49], which in turn functions as part of an antioxidant defense to protect polyunsaturated fatty acids and the damaging effects of free radicals [50], inhibiting production of proinflammatory cytokines and reactive oxygen species/reactive nitrogen species [51].

To interpret our findings, some limitations need to be taken into account. Due to budget limitation, we did not examine the effects of selenium supplementation on plasma or urine selenium, other biomarkers of systemic inflammation or oxidative stress and HbA1c. In addition, the current study was relatively of short duration of intervention. Long-term interventions might result in greater changes in circulating levels of lipid concentrations and other biomarkers of oxidative stress. It must be kept in mind that in the current study, we used LOCF method for missing values. LOCF ignores whether the participant's condition was improving or deteriorating at the time of dropout but instead freezes outcomes at the value observed before dropout (i.e., last observation). This method may introduce bias in the results, and this bias can, according to circumstance, be in either direction.

Taken together, 200 µg/day selenium supplementation for 8 weeks among patients with T2DM and CHD resulted in a significant decrease in serum insulin, HOMA-IR, HOMA-B, serum hs-CRP, a significant increase in QUICKI score, and plasma TAC concentrations; however, it did not affect FPG, lipid profiles, NO, GSH, and MDA levels.

Author Contributions

ZA contributed to conception, design, statistical analysis, and drafting of the manuscript. AF, FB MT, S-MM, M-HA, FR, and EA contributed to data collection and manuscript drafting. ZA supervised the study.

Acknowledgements

The current study was founded by a grant from the Vice-chancellor for Research, KUMS, and Iran.

Conflict of Interest

The authors declare no conflict of interest.

References

1 *Chokrungvaranon N*, *Deer J*, *Reaven PD*. Intensive glycemic control and cardiovascular disease: are there patients who may benefit? Postgrad Med 2011; 123: 114–123
2 *Rana JS*, *Dunning A*, *Achenbach S*, *Al-Mallah M*, *Budoff MJ*, *Cademartiri F*, *Callister TQ*, *Chang HJ*, *Cheng VY*, *Chinnaiyan K*, *Chow BJ*, *Cury R*, *Delago A*, *Feuchtner G*, *Hadamitzky M*, *Hausleiter J*, *Kaufmann P*, *Karlsberg RP*, *Kim YJ*, *Leipsic J*, *Labounty TM*, *Lin FY*, *Maffei E*, *Raff G*, *Villines TC*, *Shaw LJ*, *Berman DS*, *Min JK*. Differences in prevalence, extent, severity, and prognosis of coronary artery disease among patients with and without diabetes undergoing coronary computed tomography angiography: results from 10,110 individuals from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes): an InteRnational Multicenter Registry. Diabetes Care 2012; 35: 1787–1794
3 *Iijima K*, *Iimuro S*, *Shinozaki T*, *Ohashi Y*, *Sakurai T*, *Umegaki H*, *Araki A*, *Ouchi Y*, *Ito H*. Lower physical activity is a strong predictor of cardiovascular events in elderly patients with type 2 diabetes mellitus beyond traditional risk factors: the Japanese Elderly Diabetes Intervention Trial. Geriatr Gerontol Int 2012; 12 (Suppl 1): 77–87
4 *UK Prospective Diabetes Study (UKPDS) Group*. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854–865
5 *Klein EA*, *Thompson IM*, *Tangen CM*, *Crowley JJ*, *Lucia MS*, *Goodman PJ*, *Minasian LM*, *Ford LG*, *Parnes HL*, *Gaziano JM*. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2011; 306: 1549–1556
6 *Paneni F*, *Beckman JA*, *Creager MA*, *Cosentino F*. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Eur Heart J 2013; 34: 2436–2443
7 *von Bibra H*, *St John Sutton M*, *Schuster T*, *Ceriello A*, *Siegmund T*, *Schumm-Draeger PM*. Oxidative stress after a carbohydrate meal contributes to the deterioration of diastolic cardiac function in nonhypertensive insulin-treated patients with moderately well controlled type 2 diabetes. Horm Metab Res 2013; 45: 449–455
8 *Zhang X*, *Yan SM*, *Zheng HL*, *Hu DH*, *Zhang YT*, *Guan QH*, *Ding QL*. A mechanism underlying hypertensive occurrence in the metabolic syndrome: cooperative effect of oxidative stress and calcium accumulation in vascular smooth muscle cells. Horm Metab Res 2014; 46: 126–132
9 *Das UN*. Nutritional factors in the prevention and management of coronary artery disease and heart failure. Nutrition 2015; 31: 283–291
10 *Zablocka-Slowinska K*, *Dzielska E*, *Gryszkin I*, *Grajeta H*. Dietary supplementation during diabetes therapy and the potential risk of interactions. Adv Clin Exp Med 2014; 23: 939–946

11 *Eaton CB*, *Abdul Baki AR*, *Waring ME*, *Roberts MB*, *Lu B*. The association of low selenium and renal insufficiency with coronary heart disease and all-cause mortality: NHANES III follow-up study. Atherosclerosis 2010; 212: 689–694
12 *Flores-Mateo G*, *Navas-Acien A*, *Pastor-Barriuso R*, *Guallar E*. Selenium and coronary heart disease: a meta-analysis. Am J Clin Nutr 2006; 84: 762–773
13 *Stranges S*, *Marshall JR*, *Trevisan M*, *Natarajan R*, *Donahue RP*, *Combs GF*, *Farinaro E*, *Clark LC*, *Reid ME*. Effects of selenium supplementation on cardiovascular disease incidence and mortality: secondary analyses in a randomized clinical trial. Am J Epidemiol 2006; 163: 694–699
14 *Valenta J*, *Brodska H*, *Drabek T*, *Hendl J*, *Kazda A*. High-dose selenium substitution in sepsis: a prospective randomized clinical trial. Intensive Care Med 2011; 37: 808–815
15 *Jamilian M*, *Razavi M*, *Kashan ZF*, *Ghandi Y*, *Bagherian T*, *Asemi Z*. Metabolic response to selenium supplementation in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Clin Endocrinol (Oxf) 2015; 82: 885–891
16 *Alizadeh M*, *Safaeiyan A*, *Ostadrahimi A*, *Estakhri R*, *Daneghian S*, *Ghaffari A*, *Gargari BP*. 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 2012; 60: 157–168
17 *Li YB*, *Han JY*, *Jiang W*, *Wang J*. Selenium inhibits high glucose-induced cyclooxygenase-2 and P-selectin expression in vascular endothelial cells. Mol Biol Rep 2011; 38: 2301–2306
18 *He YT*, *Liu DW*, *Ding LY*, *Li Q*, *Xiao YH*. Therapeutic effects and molecular mechanisms of anti-fibrosis herbs and selenium on rats with hepatic fibrosis. World J Gastroenterol 2004; 10: 703–706
19 *Welles CC*, *Whooley MA*, *Karumanchi SA*, *Hod T*, *Thadhani R*, *Berg AH*, *Ix JH*, *Mukamal KJ*. Vitamin D deficiency and cardiovascular events in patients with coronary heart disease: data from the Heart and Soul Study. Am J Epidemiol 2014; 179: 1279–1287
20 *Jamilian M*, *Razavi M*, *Fakhrie Kashan Z*, *Ghandi Y*, *Bagherian T*, *Asemi Z*. Metabolic response to selenium supplementation in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Clin Endocrinol (Oxf) 2015; 82: 885–891
21 *Ainsworth BE*, *Haskell WL*, *Whitt MC*, *Irwin ML*, *Swartz AM*, *Strath SJ*, *O'Brien WL*, *Bassett DR Jr*, *Schmitz KH*, *Emplaincourt PO*, *Jacobs DR Jr*, *Leon AS*. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000; 32: S498–S504
22 *Pisprasert V*, *Ingram KH*, *Lopez-Davila MF*, *Munoz AJ*, *Garvey WT*. 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 2013; 36: 845–853
23 *Tatsch E*, *Bochi GV*, *Pereira Rda S*, *Kober H*, *Agertt VA*, *de Campos MM*, *Gomes P*, *Duarte MM*, *Moresco RN*. A simple and inexpensive automated technique for measurement of serum nitrite/nitrate. Clin Biochem 2011; 44: 348–350
24 *Benzie IF*, *Strain JJ*. The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": the FRAP assay. Anal Biochem 1996; 239: 70–76
25 *Beutler E*, *Gelbart T*. Plasma glutathione in health and in patients with malignant disease. J Lab Clin Med 1985; 105: 581–584
26 *Janero DR*. Malondialdehyde and thiobarbituric acid-reactivity as diagnostic indices of lipid peroxidation and peroxidative tissue injury. Free Radic Biol Med 1990; 9: 515–540
27 *Lippman SM*, *Klein EA*, *Goodman PJ*, *Lucia MS*, *Thompson IM*, *Ford LG*, *Parnes HL*, *Minasian LM*, *Gaziano JM*, *Hartline JA*, *Parsons JK*, *Bearden JD 3rd*, *Crawford ED*, *Goodman GE*, *Claudio J*, *Winquist E*, *Cook ED*, *Karp DD*, *Walther P*, *Lieber MM*, *Kristal AR*, *Darke AK*, *Arnold KB*, *Ganz PA*, *Santella RM*, *Albanes D*, *Taylor PR*, *Probstfield JL*, *Jagpal TJ*, *Crowley JJ*, *Meyskens FL Jr*, *Baker LH*, *Coltman CA Jr*. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009; 301: 39–51
28 *Stranges S*, *Marshall JR*, *Natarajan R*, *Donahue RP*, *Trevisan M*, *Combs GF*, *Cappuccio FP*, *Ceriello A*, *Reid ME*. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. Ann Intern Med 2007; 147: 217–223
29 *Rayman MP*, *Blundell-Pound G*, *Pastor-Barriuso R*, *Guallar E*, *Steinbrenner H*, *Stranges S*. A randomized trial of selenium supplementation and risk of type-2 diabetes, as assessed by plasma adiponectin. PLoS One 2012; 7: e45269
30 *Tara F*, *Maamouri G*, *Rayman MP*, *Ghayour-Mobarhan M*, *Sahebkar A*, *Yazarlu O*, *Ouladan S*, *Tavallaie S*, *Azimi-Nezhad M*, *Shakeri MT*, *Boskabadi H*, *Oladi M*, *Sangani MT*, *Razavi BS*, *Ferns G*. Selenium supplementation and the incidence of preeclampsia in pregnant Iranian women: a randomized, double-blind, placebo-controlled pilot trial. Taiwan J Obstet Gynecol 2010; 49: 181–187
31 *Faghihi T*, *Radfar M*, *Barmal M*, *Amini P*, *Qorbani M*, *Abdollahi M*, *Larijani B*. 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 2014; 21: 491–495
32 *Brigelius-Flohe R*, *Banning A*, *Kny M*, *Bol GF*. Redox events in interleukin-1 signaling. Arch Biochem Biophys 2004; 423: 66–73
33 *Douillet C*, *Tabib A*, *Bost M*, *Accominotti M*, *Borson-Chazot F*, *Ciavatti M*. A selenium supplement associated or not with vitamin E delays early renal lesions in experimental diabetes in rats. Proc Soc Exp Biol Med 1996; 211: 323–331
34 *Hwang D*, *Seo S*, *Kim Y*, *Kim C*, *Shim S*, *Jee S*, *Lee S*, *Jang M*, *Kim M*, *Yim S*, *Lee SK*, *Kang B*, *Jang I*, *Cho J*. Selenium acts as an insulin-like molecule for the down-regulation of diabetic symptoms via endoplasmic reticulum stress and insulin signalling proteins in diabetes-induced non-obese diabetic mice. J Biosci 2007; 32: 723–735
35 *Navarro-Alarcon M*, *GdlSH Lopez*, *Perez-Valero V*, *Lopez-Martinez C*. Serum and urine selenium concentrations as indicators of body status in patients with diabetes mellitus. Sci Total Environ 1999; 228: 79–85
36 *Rajpathak S*, *Rimm E*, *Morris JS*, *Hu F*. Toenail selenium and cardiovascular disease in men with diabetes. J Am Coll Nutr 2005; 24: 250–256
37 *Stapleton SR*. Selenium: an insulin-mimetic. Cell Mol Life Sci 2000; 57: 1874–1879
38 *Maritim AC*, *Sanders RA*, *Watkins JB 3rd*. Diabetes, oxidative stress, and antioxidants: a review. J Biochem Mol Toxicol 2003; 17: 24–38
39 *Steinbrenner H*, *Sies H*. Protection against reactive oxygen species by selenoproteins. Biochim Biophys Acta 2009; 1790: 1478–1485
40 *Jalili M*, *Kolahi S*, *Aref-Hosseini SR*, *Mamegani ME*, *Hekmatdoost A*. Beneficial role of antioxidants on clinical outcomes and erythrocyte antioxidant parameters in rheumatoid arthritis patients. Int J Prev Med 2014; 5: 835–840
41 *Razavi M*, *Jamilian M*, *Kashan ZF*, *Heidar Z*, *Mohseni M*, *Ghandi Y*, *Bagherian T*, *Asemi Z*. Selenium Supplementation and the Effects on Reproductive Outcomes, Biomarkers of Inflammation, and Oxidative Stress in Women with Polycystic Ovary Syndrome. Horm Metab Res 2015 Aug 12, Epub ahead of print
42 *Mishra V*, *Baines M*, *Perry SE*, *McLaughlin PJ*, *Carson J*, *Wenstone R*, *Shenkin A*. Effect of selenium supplementation on biochemical markers and outcome in critically ill patients. Clin Nutr 2007; 26: 41–50
43 *Scheurig AC*, *Thorand B*, *Fischer B*, *Heier M*, *Koenig W*. Association between the intake of vitamins and trace elements from supplements and C-reactive protein: results of the MONICA/KORA Augsburg study. Eur J Clin Nutr 2008; 62: 127–137
44 *Dunstan JA*, *Breckler L*, *Hale J*, *Lehmann H*, *Franklin P*, *Lyons G*, *Ching SY*, *Mori TA*, *Barden A*, *Prescott SL*. Supplementation with vitamins C, E, beta-carotene and selenium has no effect on anti-oxidant status and immune responses in allergic adults: a randomized controlled trial. Clin Exp Allergy 2007; 37: 180–187
45 *Madaric A*, *Kadrabova J*, *Krajcovicova-Kudlackova M*, *Valachovicova M*, *Spustova V*, *Mislanova C*, *Kajaba I*, *Blazicek P*. The effect of bioactive complex of quercetin, selenium, catechins and curcumin on cardiovascular risk markers in healthy population after a two month consumption. Bratisl Lek Listy 2013; 114: 84–87
46 *Duntas LH*. Selenium and inflammation: underlying anti-inflammatory mechanisms. Horm Metab Res 2009; 41: 443–447
47 *Seyedrezazadeh E*, *Ostadrahimi A*, *Mahboob S*, *Assadi Y*, *Ghaemmagami J*, *Pourmogaddam M*. Effect of vitamin E and selenium supplementation on oxidative stress status in pulmonary tuberculosis patients. Respirology 2008; 13: 294–298
48 *Savory LA*, *Kerr CJ*, *Whiting P*, *Finer N*, *McEneny J*, *Ashton T*. Selenium supplementation and exercise: effect on oxidant stress in overweight adults. Obesity (Silver Spring) 2012; 20: 794–801
49 *Ozturk IC*, *Batcioglu K*, *Karatas F*, *Hazneci E*, *Genc M*. Comparison of plasma malondialdehyde, glutathione, glutathione peroxidase, hydroxyproline and selenium levels in patients with vitiligo and healthy controls. Indian J Dermatol 2008; 53: 106–110
50 *Rohr-Udilova N*, *Sieghart W*, *Eferl R*, *Stoiber D*, *Bjorkhem-Bergman L*, *Eriksson LC*, *Stolze K*, *Hayden H*, *Keppler B*, *Sagmeister S*, *Grasl-Kraupp B*, *Schulte-Hermann R*, *Peck-Radosavljevic M*. Antagonistic effects of selenium and lipid peroxides on growth control in early hepatocellular carcinoma. Hepatology 2012; 55: 1112–1121
51 *Zeng J*, *Zhou J*, *Huang K*. Effect of selenium on pancreatic proinflammatory cytokines in streptozotocin-induced diabetic mice. J Nutr Biochem 2009; 20: 530–536