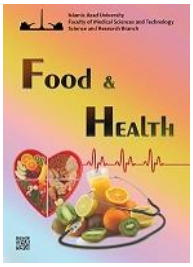

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Effect of selenium supplementation on glycemic control and lipid profile in patients with type 2 diabetes: A review on current evidence

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ABSTRACT

Diabetes is a progressive chronic disease and is considered as an important health problem, which has increased in recent years. The prevalence of diabetes in the Middle East in 2015 was 35.4 million, which more than 4.6 million people were in Iran. In this review, we specifically tried to summarize the results of clinical trials on the effects of selenium supplementation on glycemic control and lipid profile and inflammatory factors in type 2 diabetic patients. In this review, three interventional studies were included to evaluate the effect of Selenium supplementation on metabolic parameters. Serum insulin concentration and insulin resistance index were significantly reduced in two of the studies. Fasting plasma glucose and HDL cholesterol concentrations significantly increased in one study while in other studies no significant changes were observed. One of the studies showed a significant reduction in inflammatory Indicators and antioxidant capacity, one study also showed a significant decrease in lipid profiles. Selenium supplementation in patients with type 2 diabetes may have adverse effects on blood glucose homeostasis. However, it may improve lipid profile and antioxidant capacity and reduces inflammatory mediators in these patients. Therefore, in spite of the negative effects of glucose homeostasis with regard to the positive effects seen, further investigations are needed to evaluate the final effect of selenium supplementation in patients with type 2 diabetes.

1. Introduction

Diabetes is a progressive chronic disease and it is considered as an important health problem, which its prevalence has increased throughout the last decades. In recent years, countries have taken important steps to reduce diabetes, reduce its mortality and increase access to related healthcare. Previously, type 2 diabetes was a type of diabetes that was called specially for adults. However, due to the changes in lifestyle, the prevalence of diabetes in children has also increased. Type 2 diabetes for many years may not be diagnosed until it shows its complications, including heart and brain attack, renal failure, amputation of extremities, diabetic retinopathy, and neurological damages. These complications result from a combination of genetic and environmental factors. Race, family history, age-related gestational diabetes, weight gain and obesity, unhealthy diet, lack of exercise and tobacco use increase the risk of developing type 2 diabetes. Abnormally low blood sugar in people with diabetes may also lead to attacks or loss of consciousness. Diabetes and its complications along with patients and their families, as well as health and the national economy, have faced considerable problems due to medical expenses and the loss of work and wages (1). In 2015, 415 million adults in the world were diagnosed with diabetes, which is expected to increase by 642 million in 2040 or 1 in 10, 000 people (2). Estimations show that in 2015, 35.4 million people with diabetes lived in the Middle East and North Africa, of which more than 4.6 million people were in Iran (3). In most countries, diabetes expenses are accounted for between 5% to 20% of health costs. In 2015 about 720 billion was spent on treating diabetes and this figure is expected to increase 19 percent to reach 850 billion in 2040 (2). Recent studies have shown that selenium through a number of mechanisms that are not still well-established can mediate in-vivo and in-vitro insulin-like actions. These mechanisms stimulate glucose uptake and regulate metabolic

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processes such as glycolysis, gluconeogenesis, fatty acid synthesis and pentose-phosphate pathway (4). It also seems to improve oxidative stress due to its antioxidant properties. Previous studies have shown that selenium can affect glycemic control indices in patients with type 2 diabetes, including fasting blood glucose (FBG), glycosylated hemoglobin A1c (HbA1c), high-density cholesterol (HDL), and homeostasis model of assessment-estimated insulin resistance (HOMA-IR) (5). Serum levels of selenium may also be associated with total serum cholesterol, low density lipoprotein (LDL) and the prevalence of diabetes. The role of selenium in the prevention of diseases such as cardiovascular disease is widespread, including oxidative stress and subsequent NF-κB activity associated with the development of vascular complications (6). In this review study, we have specifically tried to investigate the effect of selenium supplementation on glycemic control parameters in patients with type 2 diabetes, and for this purpose, clinical trial studies were assessed to evaluate the effect of selenium supplementation on the lipid profile, FPG, HbA1c, HOMA-IR and its final consequences on general health of the patients with type 2 diabetes.

2. Methods

Electronic literature searches were conducted on Medline, Web of Science and Google Scholar until July 2017. Our search was supplemented with the search of publisher databases Elsevier, Wiley Online and SpringerLink and for any pertinent studies, we screened the references of all included studies. There were no restrictions regarding the language of publications. The search was conducted with the following words “Selenium”, in combination with Obesity, Overweight, Weight, “Insulin Resistance”, “HOMA-IR”, “Fasting Blood Glucose”, “HbA1C”, FBS, “Body Mass Index”, “Lipid Metabolism”, “Weight Gain” and “Lipid profile” among human studies.

Eligibility criteria included: Randomized clinical trials published in peer-reviewed journals and studies that used selenium supplementation in any dose with placebo for the control group. Duplicates were removed (3 articles); the relevant papers were selected in three phases. In the first and second phases, titles and abstracts of papers were screened and irrelevant papers were excluded. In the last phase, the full text of recruited papers was explored intensely to select only relevant papers. After excluding exclusive in vitro, animal studies and studies that did not report our primary outcome or fit the criteria, 3 suitable studies were identified for review, encompassing 180 subjects. Our primary outcomes were FBS or any indicator of Glucose homeostasis and lipid profile (Fig. 1).

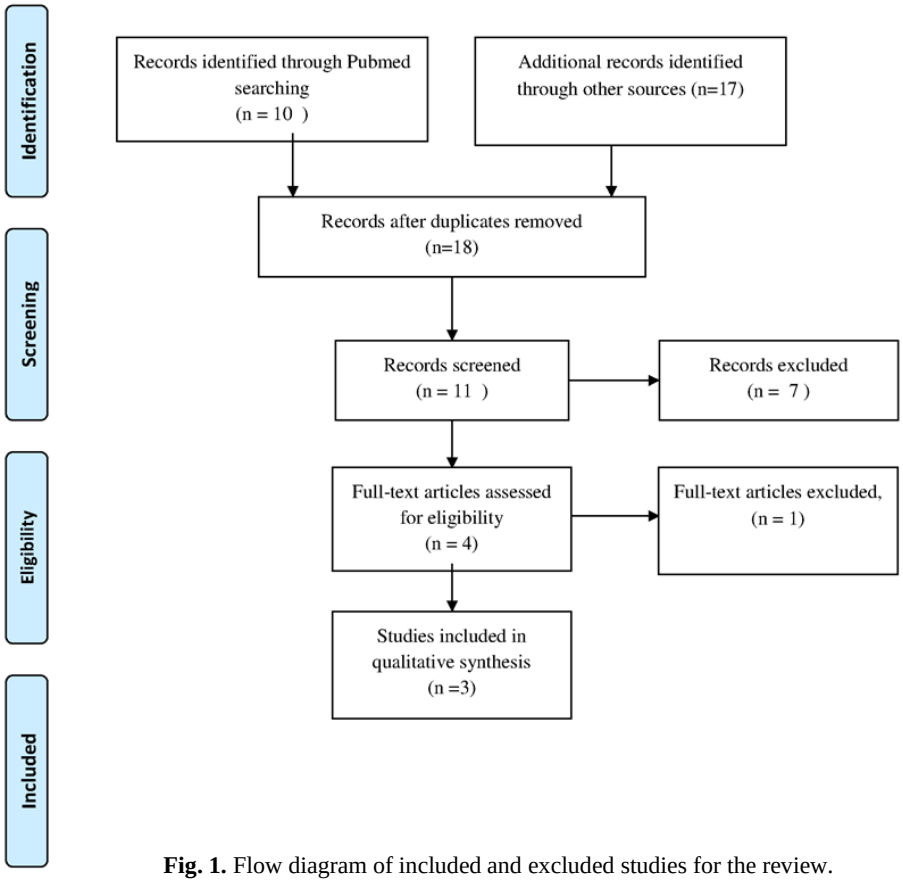

Fig. 1. Flow diagram of included and excluded studies for the review.

3. Results

In the present study, we assessed three interventional studies. The total number of subjects, in these studies, were 180 people. In the study of Faghihi and colleagues, the effect of selenium supplementation on blood glucose, lipid profiles, and oxidative stress was studied for 3 months. After this period, the comparison of the intervention group and the control group showed that in the intervention group FPG, HbA1c, and cholesterol HDL significantly increased, while other variables did not differ significantly (5). A study done in 2016 evaluated the effect of selenium supplementation on metabolic profiles, inflammatory markers, oxidative stress, insulin resistance and serum high-sensitivity C-reactive protein (hs-CRP) levels in patients with type 2 diabetes and coronary artery disease for 8 weeks. After the intervention there was a significant decrease in serum insulin, (HOMA-IR), (HOMA-B) and serum hs-CPR in the supplementation group compared with the control group, conversely, there was a significant increase in quantitative insulin sensitivity check index (QUICKI) and total antioxidant capacity (TAC) (7). The study of Jamilian and colleagues assessed the effects of selenium supplementation on glucose homeostasis parameters, lipid concentration and metabolic profile in women with polycystic ovary syndrome (PCOS) for 8 weeks. After the intervention time, parameters such as serum insulin, (HOMA-IR), homeostasis model of assessment-estimated b cell function (HOMA-B), serum triglyceride and very low density lipoprotein cholesterol (VLDL-C) concentration in the intervention group were significantly decreased in comparison to the control group, but supplementation did not result in a significant difference in FPG and other lipid profiles (8). The study of the Faghihi and colleagues was performed on 60 patients with type 2 diabetes who received an intervention at a daily dose of 200 micrograms of oral selenium. There were 33 patients in the sample group, of which 16 were male and 17 were female. The control group also had 27 patients, including 18 men and 9 women. The mean age of the sample group was 53 years and the control group was 55 years (5). In a study by Farokhian and colleagues, which was conducted in 2016, 60 patients with type 2 diabetes and coronary artery disease were studied, with an age range of 4 0-85 years old. Of these, 30 were in the intervention group and 30 were in the control group. Both groups had 20 women and 10 men and a daily dose of 200 micrograms of selenium supplement were administered to each one (7). The study of Jamilian and colleagues examined 70 women with PCOS aged 18 to 40 years old and both intervention and control groups had 35 members. The participants received 200 micrograms of selenium or placebo daily in the form of pills (8). The study conducted in 100 participants in 2011 with an average age of 53 years. 20 patients (NGT) [10 men & 10 women] in the non-diabetic group, 40 person [22 men & 18 women] in the pre-diabetic group and 40 person (25 men & 15 women) in the type 2 diabetes group. The allocation of subjects into either of these 3 groups was done by glucose tolerance test (9). All of the three studies (5, 7, 8) was double-blind clinical trials.

3.1. The effect of selenium supplementation on serum insulin concentration

In the study of Faghihi and colleagues, serum insulin concentrations in the intervention group decreased from 10.64±4.00 µIU/mL to 9.45±6.45 µIU/mL, which changed from 13.76±8.00 µIU/mL to 8.47±3.76 µIU/mL in the control group, these changes were not statistically significant in the intervention group compared to the control group (p=0.41) (5). In a study done in 2016, serum insulin changes in the intervention group were equal to -2.2±4.6 µIU/mL, while in the control group it was 3.6±8.4 µIU/mL. These changes were statistically significant in the intervention group compared to the control group (p=0.001) (7). In the study of Jamilian and colleagues, serum insulin concentrations in the intervention group decreased from 80.69±42.28 pmol/l to 50.86±32.83 pmol/l, which changed from 73.58±59.50 pmol/l to 82.65±82.50 pmol/l in the control group; these changes were statistically significant in the intervention group compared to the control group (p=0.013) (8).

3.2. Effect of selenium supplementation on insulin resistance index

In the study of Faghihi and colleagues, HOMA-IR in the intervention group decreased from 3.48±1.49 to 3.61±3.18, which changed from 5.10±3.25 to 2.87±2.00 in the control group; these changes were not statistically significant in the intervention group compared to the control group (p=0.07) (5). In the study conducted in 2016, the changes in HOMA-IR in the intervention group were -0.7±1.3, while in the control group it was 0.9±2.4, these changes were statistically significant in the intervention group compared to the control group (p=0.004) (7). In the study of Jamilian and colleagues, HOMA-IR in the intervention group decreased from 3.00±1.69 to 1.85±1.22, which changed from 2.78±2.25 to 3.20±3.42 in the control group; these changes were statistically significant in the intervention group compared to the control group (p=0.011) (8).

3.3. The effect of selenium supplementation on fasting blood glucose

In the study of Faghihi and colleagues, the plasma glucose concentration in the intervention group increased from 131.81±23.99 milligrams per deciliter to 148.15±40.72 milligrams per deciliter, which changed from 150.34±40.25 milligrams per deciliter to 130.30±45.98 milligrams per deciliter in the control group. In fact, these changes were statistically significant in the intervention group compared to the control group (p<0.01) (5). In a study done in 2016, changes in fasting plasma glucose in the intervention group were equal to -2.2±58.5 milligrams per deciliter, while in the control group it was -7.3±35.3 milligrams per deciliter, these changes were not statistically significant in the intervention group compared to the control group (p=0.69) (7). In the study of Jamilian and colleagues, fasting blood glucose levels in the

intervention group decreased from 4.91±0.52 mmol/L to 4.68±0.65 mmol/L, which changed from 5.15±0.39 mmol/L to 5.14±0.46 mmol/L in the control group. In fact, changes in the intervention group were not statistically significant compared to the control group (p=0.116) (8).

3.4. The effect of selenium supplementation on LDL cholesterol concentration

In the study of Faghihi et al., HDL cholesterol in the intervention group increased from 42.54±8.76 mg/dl to 46.15±13.56 mg/dl, which was 47.53±9.84 mg/dl to 45.69±9.06 mg/dl in the control group. These changes were statistically significant in the intervention group compared with the control group (p=0.04) (5). In the 2016 study, changes in HDL cholesterol in the intervention group were 1.3±7.7 mg/dl while in the control group it was 1.2±6 mg/dl. These changes were not significant in the intervention group compared to the control group (p=0.95) (7). In the study of Jamilian et al., HDL cholesterol in the intervention group was reduced from 1.54±0.27 mmol/L to 1.48±0.34 mmol/L. These changes in the control group reached 1.51±0.24 mmol/L to 1.57±0.38 mmol/L. these changes were not significant in the intervention group compared to the control group (p=0.091) (8). The effect of selenium supplementation on inflammatory markers. In a study done in 2016, serum hs-CRP changes in the intervention group were -1372.3±2318.8 ng/ml while the control group was -99.8±1453.6 ng/ml. These changes were significant in the intervention group compared to the control group (p=0.01). QUICKI in the intervention group increased from 0.32±0.02 to 0.33±0.02 which changed from 0.32±0.03 to 0.31±0.04 in the control group. These changes were significant in the intervention group compared to the control group (p=0.02) and (TAC) in the intervention group increased from 884.4±327.2 mmol/L to 1158.7±278.8 mmol/L which was 1029.3±322.2 mmol/L in the control group from 1156.5±384.2 mmol/L. These changes were significant in the intervention group compared to the control group (p≤0.001) (7).

3.5. Effect of selenium supplementation on lipid profiles

In the study of Jamilian and his colleagues, serum triglyceride in the intervention group decreased from 1.26±0.73 mmol/L to 1.12±0.48 mmol/L which was 1.30±0.59 mmol/l in the control group to 1.41±0.70 mmol/L. These changes were significant in the intervention group compared to the control group (p=0.025) and changes in VLDL cholesterol in the intervention group were -0.03±0.11mmol/L while in the control group it was 0.02±0.06 mmol/L. these changes were significant in the intervention group compared to the control group (p=0.025) (8).

Table 1. Characteristics of included studies.

Authors	Number of participants by gender and intervention groups	Average age	Type of study	Type of intervention	The type of substance used	Duration of intervention	Outcomes by groups
Faghihi *et al.* (5)	60 patients with type2 diabetes Selenium group: 33 people (16 men and 17 women) Placebo group: 27 people (18 men and 9 women)	Selenium group:53 Placebo group:55	Randomized, placebo-controlled trial of selenium supplementation	Parallel	200 µg selenium supplements per day	3 Months	-Serum insulin concentration, no significant changes (p=0/41) - HOMA-IR, no significant changes (p=0/07) - FPG, increased significantly (p>0/01) - HDL cholesterol, increased significantly (p=0/04)
Farrokhian *et al.* (7)	60 patients with type2 diabetes and Coronary Heart Disease Selenium group(A): 30 people (20 women and 10 men) Placebo group(B): 30 people (20 women and 10 men)	40-85	Randomized, placebo-controlled trial of selenium supplementation	Parallel	200 µg selenium supplements per day	8 Weeks	- Serum insulin concentration significant decrease (-2/2±4/6 to 3/6±8/4 (comparing selenium group to placebo group)), (p=0/001) - HOMA-IR, significant decrease (-0/7±1/3 to 0/9±2/4 (comparing selenium group to placebo group)), (p=0/004), -FPG, no significant changes, (p=0/69), -HDL cholesterol, no significant changes (p=0/95), -hs-CRP, decreased significantly, (p=0/01) - QUICKI, increased significantly (p=0/02), - TAC, increased significantly (p>0/001)
Jamilian *et al.* (8)	60 women with PCOS Selenium group: 35people Placebo group: 25people	18-40	A randomized, placebo-controlled trial of selenium supplementation	Parallel	200 µg selenium supplements per day	8 Weeks	-Serum insulin concentration, decreased significantly (p=0/013), - HOMA- IR, decreased significantly, (p=0/011) -FPG, no significant changes, (p=0/116) -HDL cholesterol, no significant changes, (p=0/091) - TG serum, decreased significantly, (p=0/025) -VLDL cholesterol, decreased significantly, (p=0/025)

4. Discussion

Based on studies conducted by the authors, this review is the first study to examine the effect of selenium supplementation on glycemic control indices and evaluating the results of studies show that selenium supplementation may affect inflammatory and lipid profile in these patients. The Study of Faqihi et al. (5), Jamilian et al. (8) and a study done in 2016 (7) examined the effects of selenium supplementation on fasting blood glucose. Selenium consumption in two of these studies did not have a significant effect on fasting blood glucose levels (7, 8) while in the study of the Faqihi et al., it was significantly increased which could be related to the increase of Pselenoproteins (Sep). Sep results in the deactivation of a major cellular energy regulator, protein kinase activated by Adenosine monophosphate. As a result, relatively low selenium concentrations in diabetic patients may be recognized as a compensatory mechanism for controlling high blood glucose levels. In addition, the theory of "redox-paradox" concept raises a decrease in insulin sensitivity with antioxidants. Indeed, after insulin binding to its receptor, it can increase the sustainability of active oxygen, species including H2O2 and acting as the second messenger and subsequently increasing insulin Signaling (5).

The Study of Faqihi et al. (5), Jamilian et al. (8), And a study was done in 2016 (7) examined the effect of selenium supplementation on insulin serum concentration and insulin resistance index. Selenium consumption in 2 of these studies resulted in a significant decrease in serum insulin concentration and insulin resistance index which could be due to inhibition of expression COX-2 and P-selectin.in addition, Selenium has similar properties to insulin (8). And may act as a potential anti-diabetes agent By improving insulin function by inhibiting inflammatory cytokines such as TNF-a and IL-1, it decreases insulin resistance (7, 8). The Study of Faqihi et al. (5), Jamilian et al.. (8), and a study done in 2016 (7) assessed the effect of selenium supplementation on HDL cholesterol concentration. Selenium consumption in two of these studies did not have a significant effect on HDL cholesterol (7, 8). The study by Jamilian et al.. investigated the effect of selenium supplementation on serum triglyceride and cholesterol VLDL concentrations, which resulted in a significant decrease in selenium used in this study. Increasing the metabolism of lipids after selenium may be due to an increase in the expression of (VLCAD) and (MCAD) and the gene of beta-oxidation (8). Selenium may induce the inhibition of abdominal fat and cholesterol accumulation through the regulation of fatty acid β-oxidation gene in adipose tissue and liver (10). A study done in 2016, evaluated the effect of selenium supplementation on serum hs-CRP and TAC. Selenium consumption in this study resulted in a significant decrease in serum hs-CRP and a significant increase in TAC (7). The beneficial effects of selenium supplementation on serum hs-CRP may be due to inhibition of NF-kappaB activity (11) and increased Selenoprotein biosynthesis (12). Increased TAC can also be attributed to Selenium's participation in the glutathione-erythrocyte system (GSH) -Px (13) which in turn acts as a part of the antioxidant defense to protect fatty acids and harmful effects of free radicals (14). Alternatively, it can inhibit the production of inflammatory cytokines and active oxygen and nitrogen species (15). In another study was done by Yang et al.. In 2011, the relationship between Sep levels, hs-CRP, (CIMT) and various clinical parameters associated with insulin resistance was evaluated in three groups: healthy (NGT), type 2 diabetes and pre- diabetes. The analysis showed a significant relationship between Sep and cardiometabolic factors such as BMI, waist circumference, systolic blood pressure, triglyceride, glucose, HbA1c, aspartate aminotransferase, and insulin resistance. In addition, the amount of Sep in circulation was high in people with impaired glucose metabolism (9).

5. Conclusion

A review of previous studies in patients with type 2 diabetes suggests that selenium supplementation on glycemic control factors may have adverse effects on Hemostasis of blood glucose. On the other hand we saw beneficial effects on the metabolic variables of insulin, triglyceride and cholesterol levels of VLDL also, a significant increase in factors such as (QUICKI) and (TAC) indicates an improvement in antioxidant capacity that can reduce the risk factors of chronic diseases in diabetic patients and improve the microvascular and macrovascular outcomes. Therefore, further studies are needed to determine the final effect of selenium supplementation in patients with type 2 diabetes.

6. Limitations

In the Study of Faqihi et al.., limitations such as the Low number of participants and the short period of follow-up interventions had great importance. Additionally, SeP changes and its association with selenium and blood glucose concentration were not evaluated in a study done in 2016 (5) with regard to budget constraints the effect of selenium supplementation on urine or plasma selenium, other markers of systemic inflammation or oxidative stress and HbA1c were not investigated. Additionally, in this study the duration of the intervention was relatively short and the (LOCF) method was used for missing values which may cause an error in the result (7). in the study of Jamilian et al., some limitations for the interpretation of data should be considered including the non-evaluation of the effects of selenium on selenium in the urine or plasma, inflammatory factors and the androgen levels associated with PCOS and the relatively short period of intervention. Long-term interventions may result in more changes in the levels of lipid profiles (8). In a study done in 2016 (7) and a study by Jamilian et al. (8), no significant side effects were observed after taking selenium supplementation.

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