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Effects of Selenium and Vitamin C Supplementation on the Glycemic Markers of Patients with Type II Diabetes: A Randomized Clinical Trial

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ABSTRACT

Introduction: Given the global prevalence of diabetes, scientists recommend supplementation with minerals and vitamins to control hyperglycemia in diabetic patients. The present study aimed to investigate the effects of separate and combined selenium and vitamin C supplementation on the glycemic markers of patients with type II diabetes.

Methods: In total, 65 patients with type II diabetes were selected from the patients referring to the Hospital and clinics in Bushehr port, Iran. After matching the samples, the patients were randomly assigned to four groups. The patients in groups one, two, and three respectively received vitamin C (1,000 mg), selenium (100 µg), and combined selenium and vitamin C daily and at the same doses for three months. In addition, group four received placebo (500 mg). Fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) were measured before and after the intervention.

Results: In group three, HbA1c and FPG increased significantly compared to the other groups and the control group. Moreover, HbA1c and FPG decreased in groups one and two after the intervention compared to the baseline, which was not considered significant.

Conclusion: According to the results, supplementation with vitamin C and selenium might induce insulin resistance in type II diabetic patients.

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Introduction

Diabetes mellitus is one of the most concerning metabolic disorders worldwide (1). According to Esteghamati et al., the prevalence of diabetes in Iran is 11.9% (2), and the prevalence rate has been estimated at 9% in Bushehr port (Iran) (3), which is significantly higher than the other provinces in Iran (4).

Vitamin C is an antioxidant that prevents tissue oxidation (5). Oxidation stress is a major contributing factor and mediator of the pathogenesis of type II diabetes (6). According to the literature, vitamin C supplementation could improve the complications caused by diabetes (7, 8) and hyperglycemia by reducing insulin resistance (9-12). However, these findings have not been confirmed in some studies (13). In a research in this regard, blood glucose was reported to increase after vitamin C supplementation (14).

Selenium (Se) is a supplement that is recommended to patients with type II diabetes for the reduction of insulin resistance (15). Selenium acts as an insulin-mimetic agent (16). It is claimed that individuals with high selenium intake are at a lower risk of developing diabetes (17). However, some animal (18, 19) and human studies (20-22) have shown a significant association between the higher intake of selenium and insulin resistance. The National Health and Nutrition Examination Survey (NHANES) revealed a positive correlation between the incidence of type II diabetes and serum selenium levels (23, 21). Another cohort study of a large sample size of northern Italian women also confirmed the positive association between serum selenium and type II diabetes (24).

Given the global prevalence of diabetes, scientists have proposed multiple approaches to the control of glycemia in diabetic patients, such

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as supplementation with minerals and vitamins. However, conflicting results have been reported in these surveys. The present study aimed to investigate the effects of separate and combined selenium and vitamin C supplementation on the glycemic markers of in type II diabetic patients.

Materials and Methods

This double-blind, placebo-controlled clinical trial was conducted during three months on 65 type II diabetic patients who were selected from the patients referring to Salman Farsi Hospital and Abolfazl Clinic in Bushehr, Iran. The patients were invited to the laboratory of Bushehr University of Medical Sciences by a letter delivered to their home and asked to fast the next morning. Initially, the research objectives were explained to the participants, and written informed consent was obtained prior to enrollment.

The inclusion criteria of the study were diagnosis with type II diabetes, age of 25-65 years, and willingness to participate in the study. The exclusion criteria were as follows: 1) fasting glucose level of >250 mg/dl; 2) other metabolic diseases; type I diabetes; 3) using antioxidant supplements within the past three months; 4) smoking habits and 5) thyroid medication, hormone replacement therapy or using antihypertensive drugs. In total, 65 patients met the inclusion criteria. The required sample size for the intervention was predicted based on glycated hemoglobin (HbA1c) changes during selenium supplementation as reported in a previous study (25).

The study protocol was approved by the Vice Chancellor for Research of Bushehr University of Medical Sciences and the ethics committee of the university (code: IR.BPUMS.REC, 1396.152). This trial has been registered in the Iranian Registry of Clinical Trials (code: IRCT20160514027879N3), and the research procedures were in line with the guidelines of the Declaration of Helsinki.

Intervention

Data collection was performed during three months, and the patients were instructed to comply with their routine diet in this period. After matching the patients in terms of age, gender, and body mass index (BMI), they were randomly assigned to four groups of 16. For the random allocation of the subjects to the intervention and groups, we used a software-generated random list (Random Allocation Software version 2). Based on the provided random sequence, the subjects were allocated to each group by choosing a numbered container. During the allocation process, each subject was assigned a unique identification code, which was used to identify the groups at the posttest stage. During the study, the main researchers were informed on this code and the corresponding treatment (supplementation/placebo). All the participants and researchers were blinded to the treatments until the randomization code was disclosed after the intervention.

The patients in groups one, two, and three respectively received vitamin C (1,000 mg), selenium (100 µg), and combined selenium and vitamin C daily at the same doses for three months. Group four was administered with calcium carbonate (500 mg) as placebo. The participants were advised not to change their routine activities and dietary habits during the study. To ensure their adherence, a dietary recall of two weekdays and one weekend was obtained from the patients before and after the intervention by a dietician. The dietary recalls were analyzed for macro- and micronutrient intake in the NUTRITIONIST IIII software version 7.0 (N-Squared Computing, Salem, OR, USA), and the activities of the participants were assessed using the valid international physical activity questionnaire (Epic-Norfolk, 2005).

The participants were visited monthly to deliver the supplements. To monitor their compliance, a supplement chart would be recorded at each visit, and the used supplement packs would be collected. Notably, some of the patients discontinued supplement consumption or chose to withdraw from the intervention (dropouts).

The body weight of the participants was measured with lightweight clothing and no shoes using an accurate scale (Seca 813 Robusta, max. 200 kg, Hamburg, Germany). In addition, the height of the patients was measured using a non-stretchable measuring tape. BMI was obtained by the division of the calculated weight by the square of height.

Biochemical Measurements

Fasting blood samples were collected at baseline and after the three-month intervention period. The samples were promptly centrifuged at 3000×g and the temperature of 4°C for 15 minutes. On the day of blood sample collection and immediately after centrifugation, the

plasma of the samples was separated and analyzed at the laboratory of the Department of Nutrition and Biochemistry.

To detect fasting plasma glucose (FPG) in the serum samples, we used the commercially available Selectra E kit autoanalyzer (Pars Azmoon, Tehran, Iran) in accordance with the instructions of the manufacturer. The limit of detection of the assay was 1.56 mg/dl, and the intra- and inter-assay coefficient of variance (CV) was 0.95%. In addition, HbA1c was measured using the commercially available Card kit (Nyco, Oslo, Norway), with the limit of detection of 0.1 mg/dl and intra- and inter-assay CV of <5%.

Statistical Analysis

Data analysis was performed in SPSS version 18 (SPSS Inc., Chicago, IL, USA) based on the intention-to-treat approach. The distribution of the variables was evaluated by probability plots and Shapiro-Wilk test, and the changes in the biochemical values were compared between the groups using the analysis of variance (ANOVA). In addition, Tukey's correction was applied in case of the presence of a main effect. The differences between the groups in terms of serum glycemic parameters were analyzed using the analysis of covariance (ANCOVA), with adjustment for age, weight, gender, dietary selenium, vitamin C, and calorie intake. Paired t-test was also used to compare the variables within the groups. In all the statistical analyses, the P-value of less than 0.05 was considered significant.

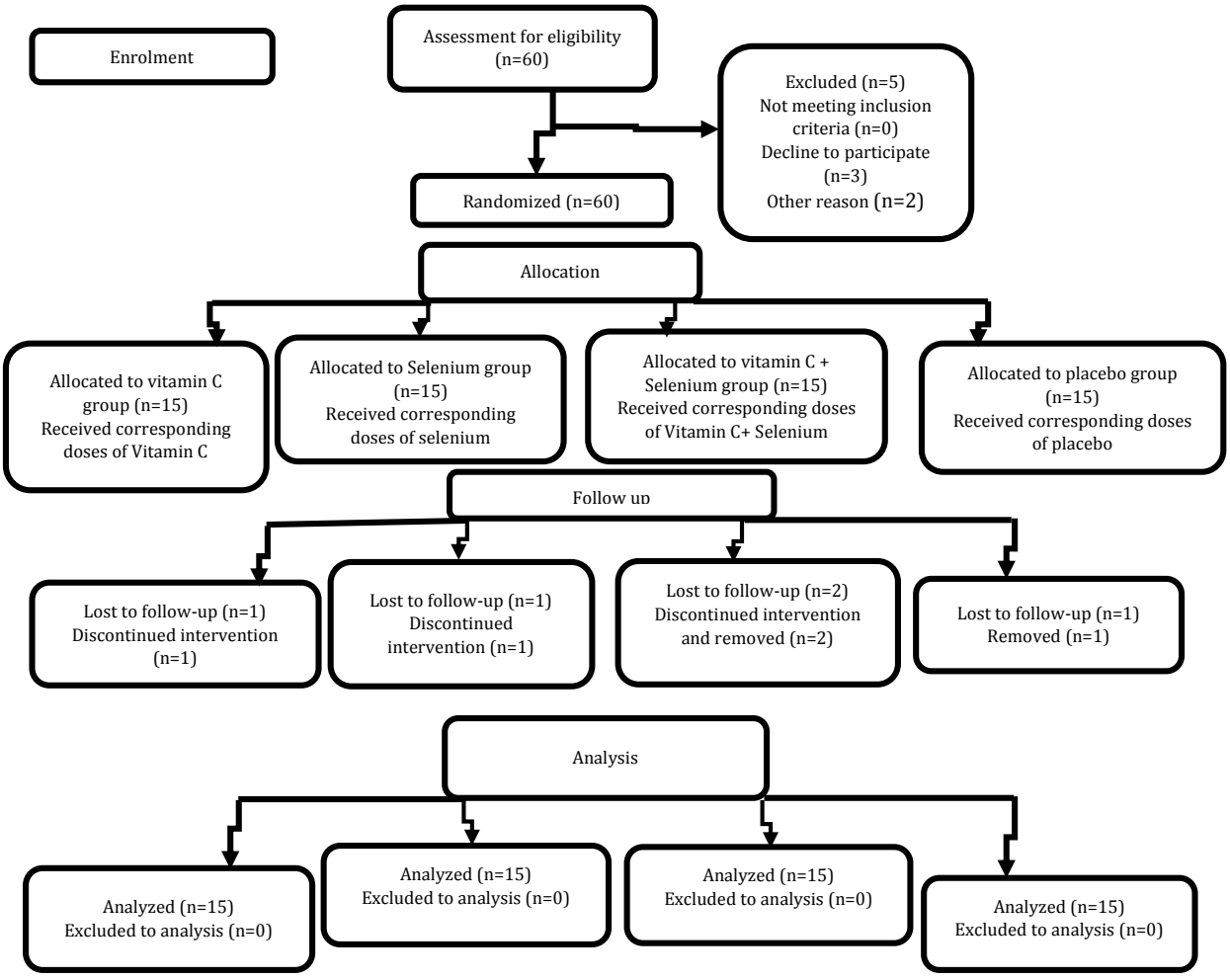

Figure 1. CONSORT flow diagram

Results

In total, 65 subjects met the inclusion criteria, and 60 completed the study. Two subjects moved from Bushehr province, and three subjects avoided continuing the project and were excluded (Figure 1). Table 1 shows the characteristics of the participants. The findings indicated no significant differences between the study groups in terms of the total energy intake, selenium and vitamin C intake, and body weight at baseline (Table 1). Moreover, no changes in were observed in the physical activity of the study groups during the study (data not shown).

The comparison results of ANCOVA between the groups indicated a more significant increase in the HbA1c level of group three compared to the other groups after adjustment for age, weight, gender, and dietary selenium and vitamin C, and calorie intake (Table 2). However, the increase in the HbA1c and FPG levels after the intervention was not considered significant in group three compared to baseline (P>0.05) (Table 3). Similarly, the reduction of the HbA1c levels in groups one and two was not considered significant after the intervention compared to baseline. No significant changes were observed in the dietary energy, selenium, and vitamin C in the study groups during the research (Table 3).

Table 1. Characteristics of the individuals (n=60). Means ± SD

Characteristic	Vitamin C group(15)	Selenium group (15)	Vitamin C + Selenium group (15)	Placebo group (15)	P-value
Gender (n)					
Male	7	6	6	7	0.86
Female	8	9	9	7	0.38
Age (years)	57	58	59	59	0.68
Weight (kg)	75.94± 10.92	77.07± 12.60	71.50± 11.18	77.00±11.18	0.37
Height	158.00±10.33	160.78±9.56	163.76±10.09	160.24±9.99	0.13
BMI (kg/m2)	29.66± 5.78	29.60± 4.16	28.27± 4.79	29.60±5.78	0.21
HbA1C	8.42±2.29	8.20±2.65	8.50±3.12	8.20±3.12	0.42
FPG	235.82± 64.32	229.60±74.40	238.20±87.63	235.82± 74.40	0.53
Dietary Calorie intake	1682±342	1634±402	1699±23	1644±28	0.59
Dietary Selenium intake	16.04±11.08	16.10±11.13	16.44±12.03	15.76±10.88	0.51
Dietary vitamin C intake	69.12±60.31	72.46±81.69	68.20±85.09	68.19±75.33	0.84

BMI; body mass index, HbA1C; glycosylated hemoglobin, FBS; Fasting plasma glucose

Table 2. Change in variables during treatment with different gums

Characteristics	Group 1 - Vitamin C		Group 2 –Selenium		Group 3 – Se + Vit C		Group 4 -placebo	
	Baseline	After 3 month	Baseline	After 3 month	Baseline	After 3 month	Baseline	After 3 month
FPG (mg/dL)	235.82± 64.32	203.15± 51.11	229.60±74.40	202.67±46.74	238.20±87.63	254.79±80.56	235.82± 74.40	238.20±74.40
HbA1c (%)	8.42±2.29	7.25±1.82	8.20±2.65	7.23±1.66	8.50±3.12	9.10±2.87	8.20±3.12	8.50±2.29
Dietary Selenium (mg/dL)	16.04±11.08	15.83±12.18	16.10±11.13	15.01±10.92	16.44±12.03	16.35±14.22	15.76±10.88	16.00±12.38
Dietary vitamin C (mg/dL)	64.12±60.31	63.19±58.03	72.46±81.69	70.56±85.09	68.20±85.09	67.91±77.23	65.19±75.33	69.99±64.31
Dietary Calorie	1682±342	1646±453	1634±402	1594±531	1699±23	1678±45	1544±28	1616±502
Weight (kg)	75.94± 10.92	75.55± 10.11	77.07± 12.60	77.00± 15.56	71.50± 11.18	71.32± 15.77	77.00±11.18	77.94±11.18
BMI (kg/m2)	29.66± 5.78	29.52± 5.71	29.60± 4.16	29.44± 5.87	28.27± 4.79	28.13± 5.59	29.60±5.78	29.31±4.00

All data are presented as mean ± SD. *significantly different from the baseline (p<0.05, paired t-test)
FPG = Fasting plasma glucose; HbA1c = Glycated hemoglobin. BMI = Body mass index.

Table 3 Differences between groups after intervention

Variables/Groups	Group 1(Vitamin C)	Group 2 (Selenium)	Group 3 (Se pluc Vit C)	Group 4 (Placebo)	*P* value
FPG (mg/dL)	-32.66± 41.07	-26.± 51.54	16.59±50.58*	2.38 ±6.99	0.04
HbA_1c (%)	-1.16±1.46	-0.96±1.84	0.59±1.80*	0.30 ±1.14	0.04
Dietary Selenium (mg/dL)	-4.17±4.56	-1.10±1.89	-0.09 ±0.42	0.24±1.05	NS
Dietary Vitamin C intake (mg/day)	-0.93±1.28	-1. 9±1.4	-0.29 ±0.88	4.80±4.04	NS
Dietary Calorie intake	-36±76	-40±.53	-21±43	72±.69	NS
Weight (kg)	-0.39±0.85	-0.07±0.69	-0.18±0.47	0.94±1.06	NS
BMI (kg/m^2)	-0.14 ±0.99	-0.16 ±0.28	-0.14±.16	-0.29±0.35	NS

Data are presented as mean ± SD. One way ANOVA was used to assess the effect of different treatment between groups on glycemic, anthropometric indices and Dietary intake. Tukey *post hoc* test was applied wherever an effect was observed. *Significantly different compared to the control group.

FPG = Fasting plasma glucose; HbA1c = Glycated hemoglobin; BMI = Body mass index

Discussion

The results of the present study indicated a significant increase in the HbA1c and FPG levels of the diabetic patients supplemented with selenium and vitamin C. However, neither selenium nor vitamin c alone could increase HbA1c. In line with our findings, several reports have indicated that long-term dietary selenium supplementation could increase the incidence of type II diabetes (23, 26, 27). For instance, Czernichow et al. stated that supplementation with 100 micrograms of selenium and 120 milligrams of vitamin C could significantly increase blood glucose (28), In addition, Hercberg et al. and Zhang et al. have confirmed that long-term daily supplementation with selenium and vitamin C may significantly increase the risk of metabolic syndrome (29, 30). Consistently, numerous findings have shown an association between high levels of plasma selenium and elevated FPG (21, 23, 24, 27, 31).

According to the animal studies in this regard, the mechanisms that may explain the pathway of destruction in insulin sensitivity following the prescription of a high dose of selenium are glycolysis in the muscles (31) and release of glucagon following high selenium intake (33). Furthermore, some human studies have indicated a positive, significant correlation between selenium-dependent enzyme activity (glutathione peroxidases [GPx]) and insulin resistance (34). Accordingly, selenium intake of more than 55 micrograms per day (34) could lead to the overexpression of GPx1 and the subsequent production of reactive oxygen species (ROS) (36-38).

High levels of ROS reduce some transcription factors (e.g., mitochondrial uncoupling protein 2), which are essential to the signaling process in pancreatic β cells. In fact, β cell apoptosis has been reported to occur in the presence of high ROS (39, 40). In addition, excess ROS is associated with insulin resistance (6, 41) since increased ROS **suppress** serine/threonine kinases, which in turn **reduces** the phosphorylated insulin receptor (42) and terminates insulin **sensitivity** (43-46). Some studies have also shown that high selenium intake triggers the production of forkhead box protein O1, which is a transcription factor that blocks the insulin signaling pathway, thereby suppressing the production of the enzymes involved in glucose catabolism (47).

Low doses of selenium could stimulate glucose uptake in the adipocytes by activating glucose transporters (15, 41). However, high-dose selenium supplementation or the ingestion of other elements that enhance selenium uptake may not have beneficial effects in this regard. In a study, Pinto et al. (47) reported increased plasma insulin following 16 weeks of supplementation with 0.50 milligrams of selenium per kilogram compared to the concentration of 0.17 mg/kg in an animal model. In addition, the findings of Rasekh et al. (48) demonstrated that the peritoneal injection of selenium to rats led to hyperglycemia in a dose-dependent manner. Therefore, it could be inferred that selenium has a narrow therapeutic index (49, 50).

Some agents such as vitamin C could increase selenium uptake (51), and it is assumed that the consumption of vitamin C with selenium in the present study led to increased selenium absorption. In our previous study, a significant increase was observed in GPX following the administration of vitamin C (200 mg/d) (52). In the current research, the synergistic effects of selenium and vitamin C on GPX and ROS might explain the effects of selenium and vitamin C combination on insulin resistance in the type II

diabetic patients. Notably, vitamin C has antioxidative and pro-oxidative properties. In an *in-vivo* study, Podmore et al. reported the potential pro-oxidative effects of vitamin C on DNA base oxidation (53). Another research also indicated that the co-supplementation of vitamin C and iron led to the oxidative destruction of the DNA (54). It is hypothesized that the pro-oxidative properties of vitamin C may increases the ability of selenium in inducing ROS production.

The main limitation of the present study was that we did not measure serum selenium, which could have further validated our findings and should be considered in further investigations.

Conclusion

According to the results, supplementation with vitamin C and selenium could induce insulin resistance in type II diabetic patients.

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Conflicts of Interest

None declared.

References

1. American diabetes association. glycemic targets: standards of medical care in diabetes—2021. Diabetes Care. 2021;44(Supplement 1):S73-S84.
2. Esteghamati A, Larijani B, Aghajani MH, Ghaemi F, Kermanchi J, Shahrami A, et al. Diabetes in Iran: prospective analysis from first Nationwide diabetes report of National Program for prevention and control of diabetes (NPPCD-2016). Sci Rep. 2017;7(1):13461.
3. Soltanian AR, Bahreini F, Afkhami-Ardekani M. People awareness about diabetes disease and its complications among aged 18 years and older in Bushehr port inhabitants (Iran). Diabetes Metab Syndr. 2007;1(4):245-9.
4. Golozar A, Khademi H, Kamangar F, Poutschi H, Islami F, Abnet CC, et al. Diabetes mellitus and its correlates in an Iranian adult population. PLoS One. 2011;6(10):e26725.
5. Tamari Y, Nawata H, Inoue E, Yoshimura A, Yoshii H, Kashino G, et al. Protective roles of ascorbic acid in oxidative stress induced by depletion of superoxide dismutase in vertebrate cells. Free Radic. Res. 2013;47(1):1-7.
6. Frei B, England L, Ames BN. Ascorbate is an outstanding antioxidant in human blood plasma. Proc Natl Acad Sci. 1989;86(16):6377-81.
7. Chakraborty S, Nandi A, Mukhopadhyay M, Mukhopadhyay CK, Chatterjee IB. Ascorbate protects guinea pig tissues against lipid peroxidation. Free Radic Biol Med. 1994;16(4):417-26.
8. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature. 2006;440(7086):944-8.
9. Paolisso G, D'Amore A, Balbi V, Volpe C, Galzerano D, Giugliano D, et al. Plasma vitamin C affects glucose homeostasis in healthy subjects and in non-insulin-dependent diabetics. Am J Physiol Endocrinol. 1994;266(2):E261-E8.
10. Paolisso G, Balbi V, Volpe C, Varricchio G, Gambardella A, Saccomanno F, et al. Metabolic benefits deriving from chronic vitamin C supplementation in aged non-insulin dependent diabetics. J Am Coll Nutr. 1995;14(4):387-92.
11. Eriksson J, Kohvakka A. Magnesium and ascorbic acid supplementation in diabetes mellitus. Ann Nutr Meta. 1995;39(4):217-23.
12. Afkhami-Ardekani M, Shojaoddiny-Ardekani A. Effect of vitamin C on blood glucose, serum lipids & serum insulin in type 2 diabetes patients. Indian J Med Res. 2007;126(5):471.
13. Gillani SW, Sulaiman SAS, Abdul MIM, Baig MR. Combined effect of metformin with ascorbic acid versus acetyl salicylic acid on diabetes-related cardiovascular complication; a 12-month single blind multicenter randomized control trial. Cardiovasc Diabetol. 2017;16(1):103.
14. Ashor A, Werner A, Lara J, Willis N, Mathers J, Siervo M. Effects of vitamin C supplementation on glycaemic control: a systematic review and meta-analysis of randomised controlled trials. Eur J Clin Nutr. 2017;71(12):1371-80.
15. Bishop N, Schorah C, Wales J. The effect of vitamin C supplementation on diabetic hyperlipidaemia: a double blind, crossover study. Diabet Med. 1985;2(2):121-4.
16. Branch DR. High-dose vitamin C supplementation increases plasma glucose. Diabetes Care. 1999;22(7):1218-9.
17. Ezaki O. The insulin-like effects of selenate in rat adipocytes. J Biol Chem. 1990;265(2):1124-8.
18. Stapleton S. Selenium: an insulin mimetic. Cell Mol Life Sci. 2000;57(13-14):1874-9.
19. Rajpathak S, Rimm E, Morris JS, Hu F. Toenail selenium and cardiovascular disease in men with diabetes. J Am Coll Nutr. 2005;24(4):250-6.
20. Mueller AS, Pallauf J, Rafael J. The chemical form of selenium affects insulinomimetic properties of the trace element: investigations in type II diabetic dbdb mice. J Nutr Biochem. 2003;14(11):637-47.
21. Shimizu R, Ueno H, Okuno T, Sakazaki F, Nakamuro K. Effect of sodium selenite supplementation on glucose intolerance and pancreatic oxidative stress in type 2 diabetic mice under different selenium status. J Health Sc. 2009;55(2):271-80.

22. Simić A, Hansen AF, Åsvold BO, Romundstad PR, Midthjell K, Syversen T, et al. Trace element status in patients with type 2 diabetes in Norway: The HUNT3 Survey. J Trace Elem Med Biol. 2017;41:91-8.
23. Laclaustra M, Navas-Acien A, Stranges S, Ordovas JM, Guallar E. Serum selenium concentrations and diabetes in US adults: national health and nutrition examination survey (NHANES) 2003–2004. Environ Health Perspect. 2009;117(9):1409-13.
24. Yuan Z, Xu X, Ye H, Jin L, Zhang X, Zhu Y. High levels of plasma selenium are associated with metabolic syndrome and elevated fasting plasma glucose in a Chinese population: a case-control study. J Trace Elem Med Biol. 2015;32:189-94.
25. Bleys J, Navas-Acien A, Guallar E. Serum selenium and diabetes in US adults. Diabetes care. 2007;30(4):829-34.
26. Stranges S, Sieri S, Vinceti M, Grioni S, Guallar E, Laclaustra M, et al. A prospective study of dietary selenium intake and risk of type 2 diabetes. BMC Public Health. 2010;10(1):564.
27. Dakhale GN, Chaudhari HV, Shrivastava M. Supplementation of vitamin C reduces blood glucose and improves glycosylated hemoglobin in type 2 diabetes mellitus: a randomized, double-blind study. Adv Pharmacol Sci. 2011;2011:195271.
28. Stranges S, Marshall JR, Natarajan R, Donahue RP, Trevisan M, Combs GF, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. Ann Intern Med. 2007;147(4):217-23.
29. Bleys J, Navas-Acien A, Guallar E. Selenium and diabetes: more bad news for supplements. Ann Intern Med. 2007;147(4):271-2.
30. Czernichow S, Couthouis A, Bertrais S, Vergnaud AC, Dauchet L, Galan P, et al. Antioxidant supplementation does not affect fasting plasma glucose in the Supplementation with Antioxidant Vitamins and Minerals (SU.VI.MAX) study in France: association with dietary intake and plasma concentrations. Am J Clin Nutr. 2006;84(2):395-9.
31. Hercberg S, Bertrais S, Czernichow S, Noisette N, Galan P, Jaouen A, et al. Alterations of the lipid profile after 7.5 years of low-dose antioxidant supplementation in the SU.VI.MAX Study. Lipids. 2005;40(4):335-42.
32. Zhang L, Gail MH, Wang YQ, Brown LM, Pan KF, Ma JL, et al. 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.2006;84(4):912-9.
33. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al. 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(1):39-51.
34. Yang K-C, Lee L-T, Lee Y-S, Huang H-Y, Chen C-Y, Huang K-C. Serum selenium concentration is associated with metabolic factors in the elderly: a cross-sectional study. Nutr Metab. 2010;7(1):38.
35. Furnsinn C, Englisch R, Ebner K, Nowotny P, Vogl C, Waldhausl W. Insulin-like vs. non-insulin-like stimulation of glucose metabolism by vanadium, tungsten, and selenium compounds in rat muscle. Life Sci. 1996;59(23):1989-2000.
36. Satyanarayana S, Sekhar JR, Kumar KE, Shannika LB, Rajanna B, Rajanna S. Influence of selenium (antioxidant) on gliclazide induced hypoglycaemia/anti hyperglycaemia in normal/alloxan-induced diabetic rats. Mol Cell Biochem. 2006;283(1-2):123-7.
37. Chen X, Scholl TO, Leskiw MJ, Donaldson MR, Stein TP. Association of glutathione peroxidase activity with insulin resistance and dietary fat intake during normal pregnancy. J Clin Endocrinol Metab. 2003;88(12):5963-8.
38. Burk RF, Norsworthy BK, Hill KE, Motley AK, Byrne DW. Effects of chemical form of selenium on plasma biomarkers in a high-dose human supplementation trial. Cancer Epidemiol Biomarkers Prev. 2006;15(4):804-10.
39. McClung JP, Roneker CA, Mu W, Lisk DJ, Langlais P, Liu F, et al. Development of insulin resistance and obesity in mice overexpressing cellular glutathione peroxidase. Proc Natl Acad Sci. 2004;101(24):8852-7.
40. Pepper MP, Vatamaniuk MZ, Yan X, Roneker CA, Lei XG. Impacts of dietary selenium deficiency on metabolic phenotypes of diet-restricted GPX1-overexpressing mice. Antioxid Redox Signal. 2011;14(3):383-90.
41. Wang X, Vatamaniuk MZ, Roneker CA, Pepper MP, Hu LG, Simmons RA, et al. Knockouts of SOD1 and GPX1 exert different impacts on murine islet function and pancreatic integrity. Antioxid Redox Signal. 2011;14(3):391-401.
42. Brigelius-Flohe R, Banning A, Schnurr K. Selenium-dependent enzymes in endothelial cell function. Antioxid Redox Signal. 2003;5(2):205-15.
43. Esposito LA, Kokoszka JE, Waymire KG, Cottrell B, MacGregor GR, Wallace DC. Mitochondrial oxidative stress in mice lacking the glutathione peroxidase-1 gene. Free Radic. Biol. Med. 2000;28(5):754-66.
44. Rhee SG. H2O2, a necessary evil for cell signaling. Science. 2006;312(5782):1882-3.
45. Rhee SG. Measuring H 2 O 2 produced in response to cell surface receptor activation. Nat Chem Biol. 2007;3(5):244-6.
46. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. Endocr Rev. 2002;23(5):599-622.
47. Evans JL, Maddux BA, Goldfine ID. The molecular basis for oxidative stress-induced insulin resistance. Antioxid Redox Sign. 2005;7(7-8):1040-52.
48. Simon AR, Rai U, Fanburg BL, Cochran BH. Activation of the JAK-STAT pathway by reactive

oxygen species. Am J Physiol Cell Physiol. 1998;275(6):C1640-52.
49. Storz G, Tartaglia LA, Ames BN. Transcriptional regulator of oxidative stress-inducible genes: direct activation by oxidation. Science. 1990;248(4952):189-94.
50. Zheng M, Aslund F, Storz G. Activation of the OxyR transcription factor by reversible disulfide bond formation. Science. 1998;279(5357):1718-21.
51. Hayes GR, Lockwood DH. Role of insulin receptor phosphorylation in the insulinomimetic effects of hydrogen peroxide. Proc Natl Acad Sci U S A 1987;84(22):8115-9.
52. Pinto A, Juniper DT, Sanil M, Morgan L, Clark L, Sies H, et al. Supranutritional selenium induces alterations in molecular targets related to energy metabolism in skeletal muscle and visceral adipose tissue of pigs. Toxicol Lett. 2012;114:47-54.
53. Rasekh HR, Potmis RA, Nonavinakere VK, Early JL, Iszard MB. Effect of selenium on plasma glucose of rats: role of insulin and glucocorticoids. Toxicol Lett. 1991;58(2):199-207.
54. Whanger P, Vendeland S, Park YC, Xia Y. Metabolism of subtoxic levels of selenium in animals and humans. Ann Clin Lab Sci. 1996;26(2):99-113.
55. Vinceti M, Wei ET, Malagoli C, Bergomi M, Vivoli G. Adverse health effects of selenium in humans Rev Environ Health. 2001;16(4):233-51.
56. Vitamin C Can Promote Selenium Utilization. Nutr Rev. 1990;48(7):290-1.
57. Mahmoudabadi MM, Rahbar AR. Effect of EPA and vitamin C on superoxide dismutase, glutathione peroxidase, total antioxidant capacity and malondialdehyde in type 2 diabetic patients. Oman Med J. 2014;29(1):39-45.
58. Podmore ID, Griffiths HR, Herbert KE, Mistry N, Mistry P, Lunec J. Vitamin C exhibits pro-oxidant properties. Nature. 1998 ;392(6676):559.
59. Rehman A, Collis CS, Yang M, Kelly M, Diplock AT, Halliwell B, et al. The effects of iron and vitamin C co-supplementation on oxidative damage to DNA in healthy volunteers. Biochem Biophys Res Commun. 1998;246(1):293-8.