Serum Selenium Status in Patients with Type 2 Diabetes and Control Group

Zahra Heidari[1], Zahra Sepehri[2] & Aleme Doostdar[1]

[1] Department of Endocrinology and Metabolism, Zahedan University of Medical Sciences, Zahedan, Iran

[2] Department of Internal Medicine, Zabol University of Medical Sciences, Zabol, Iran

Correspondence: Zahra Heidari, Department of Endocrinology and Metabolism, Zahedan University of Medical Sciences, Zahedan, Iran. E-mail: z.heidari10@yahoo.com

Abstract

In addition to known risk factors, the role of different micronutrients such as selenium in diabetes incidence has been proposed. Some previous studies have shown an association of selenium deficiency and type 2 diabetes mellitus, while other studies have not confirmed such a relationship. The aim of this study was to evaluate serum level of selenium in patients with Type 2 diabetes compared with the control group. This cross-sectional study was carried out on patients with type 2 diabetes in Zahedan, southeastern Iran. One hundred newly diagnosed type 2 diabetic patients were evaluated for serum selenium level. One hundred subjects from the general population who had normal fasting blood sugar levels were selected as the control group. The control group subjects were matched in pairs with each of patients on the basis of sex, age (± one year), and body mass index (±1). Serum level of selenium was determined by spectrometry method. Results were compared using t-test. The mean serum level of selenium in patients was 94.47±18.07 μg/L whereas in control group was 142.79±23.67 μg/L. The mean serum level of selenium was significantly different between the two groups (P<0.001). Serum levels of selenium in diabetic patients with significant difference statistically were lower than the control group. In order to evaluate serum level of selenium in patients with diabetes, studies with larger sample size are required. Likewise, prospective studies along with selenium supplementation and investigating its effect on incidence of diabetes are accordingly needed.

Keywords: selenium, Type 2 diabetes mellitus

1. Introduction

Type 2 diabetes mellitus accounts for about 90% of all diagnosed cases of diabetes and is characterized by hyperglycemia, insulin resistance and relative decline in insulin secretion. Type 2 diabetes is a debilitating and progressive disease whose prevalence has increased in recent decades (Engelgau et al., 2004). According to previous studies, Iran is facing an increasing prevalence of diabetes; therefore, the prevalence of disease in Iran population reaches to 7% (Esteghamati et al., 2008). Type 2 diabetes is characterized by varying degrees of insulin resistance in peripheral tissue such as muscle, liver and adipose tissue as well as relative decrease in insulin secretion by beta cells that genetic and environmental factors are involved in each of these factors (Stumvoll, Goldstein, & van Haeften, 2005; Li et al., 2004). The most important risk factors for type 2 diabetes are high energy intake, aging, sedentary lifestyle and obesity. In addition to these known risk factors, the role of different micronutrients such as selenium in incidence of diabetes has also been proposed.

Selenium is an essential mineral and micronutrient, with antioxidant properties which is able to change immune and inflammatory response. Selenium is an essential component of glutathione peroxidase enzyme that plays a role in the detoxification of free oxygen radicals and other toxic oxygen derivatives. Functional defect in glutathione peroxidase can cause damage to cell membranes (Steinbrenner, Speckmann, & Klotz, 2016; Oztürk et al., 2015; Sedighi, Makhlough, Shokrzadeh, & Hoorshad, 2014; Rayman, 2000). Selenium induces a decrease in serum levels of glucose in the rats treated with this element. In addition, serum levels of metabolites that cause liver damage and disturbance in lipid metabolism are markedly reduced in these rats (Zou, Qiu, Chen, Dou, & Liang, 2016; Hwang et al., 2007). Diabetes is usually associated with increased free radical production (Sailaja, Baskar, & Saralakumari, 2003; Baynes & Thorpe, 1999) or decreased antioxidant defenses (Maritim, Sanders, & Watkins, 2003). Increased free radicals cause damage to cellular proteins, membranes lipids and nucleic acid and ultimately

cell death. In diabetes, hyperglycemia not only increases the production of free radicals but also decreases the antioxidant defense mechanisms (Saxena, Srivastava, & Baquer, 1993).

Selenium acts like insulin on glucose homeostasis in previous studies (Gouaref, Bellahsene, Zekri, Alamir, & Koceir, 2016; Al-Quraishy, Dkhil, & Abdel Moneim, 2015; Chen, Qiu, Zou, Dou, & Liang, 2015; Becker et al., 1996). Diabetes associated oxidative stress is responsible for secondary complications of diabetes (González de Vega, Fernández-Sánchez, Fernández, Álvarez Menéndez, & Sanz-Medel, 2016; Kahya, Nazıroğlu, & Övey, 2016) so antioxidant supplements such as selenium seems to be highly desirable for the treatment of this disease and its complications (Kahya, Naziroğlu, & Çiğ, 2015; Feng et al., 2015). However, other studies have shown that there is a positive correlation between serum level of selenium and diabetes incidence (Laclaustra, Navas-Acien, Stranges, M. Ordovas, & Guallar, 2009; Stranges et al., 2007; Steinbrenner, Speckmann, Pinto, & Sies, 2011; Lu et al., 2016; Thompson et al., 2016; Farrokhian et al., 2016; Rotter et al., 2015; Bleys, Navas-Acien, & Guallar ,2007; Mueller, Mueller, Wolf, & Pallauf ,2009).

The existing literature data regarding the role of serum selenium levels in type 2 diabetes and its complications are controversial, thus we conducted this study in order to investigate whether selenium levels differ in Type 2 diabetic patients and control group.

2. Materials and Methods

The present study was conducted using case-control method on patients with type 2 diabetes referring to Imam Ali Hospital in Zahedan, between October 2015 and February 2016. Patients with type 2 diabetes who were at least 30 years old were continuously enrolled in the study. Patients data such as age, gender, type of diabetes, duration of diabetes, incidence of other diseases, drug history and body mass index were recorded. Diabetes is defined as fasting plasma glucose $\geq$ 126 mg per deciliter (two times), oral glucose tolerance test $\geq$ 200 mg per deciliter, glycated hemoglobin $\geq$ 6.5 and random blood sugar > 200 mg per deciliter in the presence of symptoms. Pregnant patients as well as patients with liver disease, kidney disease, hyper or hypothyroidism, acute coronary syndrome, stroke, cancer or patients who take vitamin supplements were excluded. Finally, 100 patients with type 2 diabetes were enrolled in the study. For each patient in case group one person who was matched in terms of age ($\pm$ one year), sex and body mass index ($\pm$ 1) was selected among healthy volunteers of blood donors referred to Zahedan Blood Transfusion Organization as a control group. In the control group, fasting plasma glucose was measured to rule out diabetes, if their fasting blood sugar was less than 100 they were enrolled as controls. Body weight without shoes using a digital scale and height in standing position was measured using a stadiometer. Body mass index was determined using this formula: weight in kilograms was divided by the square of height in meters. All blood samples were collected between 8 and 9 am and after 8 hours fasting and stored frozen at -70 until examination. Selenium using spectrometry method was measured [Graphite furnace atomic absorption spectrometry Varian, Australia (Spectr AA 240fs, 2009)]. Reference range for selenium was 70-150 µg/L. Glucose was measured with glucose oxidase technique (Pars Iran test). Quantitative variables were expressed as mean (and standard deviation) and qualitative variables were expressed as a percentage, t -test and Mann-Whitney U-test were used to compare quantitative variables and Chi-Square was used to compare qualitative variables. Multivariate logistic regression analysis was done with diabetes as the dependent variable and age, body mass index, serum level of selenium as independent variables. All the analysis were performed by software STATA version 12 (Stata Corporation, College Station, TX). Informed written consent was obtained from all subjects. The Research was approved on Ethics Committee of Medical Sciences (ethical code number IR.ZAUMS.REC.1392.56).

3. Results

In this study, 200 patients (100 with diabetes and 100 healthy subjects) who met the inclusion and exclusion criteria were registered. Gender distribution between two groups was equal, as 50 males and 50 females in each case and control group. The subjects in case group were diabetics and participants in control group were healthy subjects. The average age of the participants in the study was 44.32±10.10 years. The average age of study groups was 44.54±10.50 years in the case group and 44.40±10.43 years in the control group. Using Independent sample t-test there was no statistically significant difference between the two groups in terms of age (P=0.8). The mean BMI (body mass index) in case group was 27.05±4.22 kg/ m² and controls 27.11±4.15 kg/ m². Using Independent sample t-test there was no statistically significant difference between BMI of both groups (P= 0.9).

Table 1. Characteristics of subjects in each group

Variable		Frequency		Percentage	
		Case	Control	Case	Control
Gender	Male	50	50	50	50
	female	50	50	50	50
Age (yera)	<40	25	25	25	25
	40-60	61	61	61	61
	>60	14	14	14	14
BMI (kg/m2)	<18.5	0	0	0	0
	18.5-24.9	24	24	24	24
	25-29.9	48	48	48	48
	≥30	28	28	28	28

As shown in Table 2, the mean serum level of selenium in case group was 94.47±18.07 mcg per liter (μg/L) and in the control group was 142.79±23.67 μg/L. Mean serum level of selenium in both case and control groups showed significant difference (P<0.001).

Table 2. Comparison of selenium serum level in participants in the study based on group

Variable	Group	Mean±SD	Range	p-value
Serum selenium levels	Case	94.47±18.07	56.10-156.40	<0.001
(mcg per dL)	control	142.79±23.67	79.82-162.40	

SD: standard deviation.

Selenium deficiency has been effective in diabetes (P=0.006). Also, people who had higher serum selenium levels, their chance to be non-diabetic was 19.33 times higher (Table 3).

Table 3. Effective factors in diabetes

Variable		Patients with diabetes (frequency)	Healthy subject (Frequency)	Total (frequency)	OR	CI	p-value
Gender	Male	50	50	100	1	0.57-1.74	0.55
	female	50	50	100			
Age (year)	<40	25	24	49	1.05	0.55-2.01	0.50
	≥40	75	76	151			
BMI	<25	24	24	48	1	0.52-1.91	0.56
	≥25	76	76	152			
Selenium Deficiency	Yes <60 μg/dl	47	22	69	19.33	2.31-161.56	0.006
	No >60 μg/dl	53	78	131			

OR: oddsratio, CI: confidence interval.

4. Discussion

In this descriptive cross sectional study, a total of 200 patients (100 patients with type 2 diabetes and 100 healthy individuals), after applying inclusion and exclusion criteria were enrolled. Mean serum level of selenium in the case and control groups was significantly different.

These results are in accordance with some previous studies (Rajpathak, Rimm, Morris, & Hu, 2005; Kilinc, Guven, Ezer, Ertas, & Coskun, 2008; Yadav et al., 2016; Ubajaka et al., 2015). In a study (Kruse-Jarres & Rukgauer, 2000), serum levels of selenium in both diabetics and non-diabetics control group was measured in three components of plasma, erythrocytes and complete blood that in all three components, selenium concentration was lower in the diabetic group and this decrease is more clearly shown in erythrocytes . Additionally, in another study, serum level of selenium in patients with diabetes mellitus was determined compared with the control group. In the diabetic group that included 150 diabetic patients aged 11 to 60 years, the average concentration of plasma selenium significantly lower than the control group (Ruiz, Alegria, Barbera, Farre, & Lagarda, 1998). Similar to our study, in a study conducted in 2012 in diabetic patients aged 40 to 60 years, serum level of selenium in the diabetic group showed a significant decrease in comparison to the control group (Kumar, 2012).

But, in other studies the increasing serum level of selenium was associated with an increased incidence of diabetes (Wang, Yang, Wei, Lei, & Zeng, 2016; Ogawa-Wong, Berry, & Seale, 2016; Bleys, Navas-Acien, & Guallar, 2007). Concentration and activity of glutathione peroxidase and other selenoproteins increases with increasing selenium intake until dose-response relationship reached an equilibrium state. The maximum rate of this condition in serum levels is 70-90 µg/L. In plasma levels higher than this amount, the selenomethionine entry into albumin and other proteins increases and concentration or activity of glutathione peroxidase does not change (Burk, 2002). Animal studies show that diets containing abundant selenium may stimulate the secretion of glucagon leading to hyperglycemia (Satyanarayana et al., 2006). Selenium enters into the structure of selenoproteins such as selenocysteine. Selenoproteins are responsible for the biological function of selenium and specific selenoproteins such as glutathione peroxidase, selenoprotein P and thioredoxin reductase are important antioxidant enzymes (Rayman, 2000).

In addition to the effect of antioxidant, selenium has anti-diabetic and insulin-like effects (Wang et al., 2016; Gurbanov, Bilgin, & Severcan, 2016; Mueller & Pallauf, 2006). In a study conducted in 2013 serum selenium level was measured in patients with diabetes in different countries. According to this study, in France, China and Italy high concentrations of selenium was associated with an increased incidence of diabetes, but in America increased selenium was associated with reducing the diabetes. In Singapore, no relationship between serum selenium and diabetes was reported (Rayman, 2013). Such different results in different countries may be due to various reasons, including ethnic differences and various confounding factors that need further studies. Also, Diet is the most important source of selenium in most countries (Wei et al., 2015). Soil selenium content is different in various geographical regions which can lead to different serum selenium levels among the various countries. For example, in volcanic regions, low soil selenium causes selenium deficiency in these populations (Thomson, 2004).

The lack of measurement of selenium content in the diet and urine was one of the limitations of this study. Another limitation of this study is its cross-sectional nature, which naturally cannot show the causal relationship. But the sample size is relatively acceptable and matching case and control groups based on gender, age and body mass index as pairs is of the strength of this study. Prospective studies with larger sample size and selenium supplementation and evaluation of its effect on the incidence of diabetes, can be effective to to further clarify the role of this element in the incidence and pathogenesis of diabetes.

5. Conclusion

Serum levels of selenium in diabetic patients with statistically significant difference statistically were lower than the control group. Studies with larger sample size to evaluate serum level of selenium in patients with diabetes are therefore, required. Prospective studies along with selenium supplementation and investigating its effect on incidence of diabetes are also needed.

Competing Interests Statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

Al-Quraishy, S., Dkhil, M. A., & Abdel Moneim, A. E. (2015). Anti-hyperglycemic activity of selenium nanoparticles in streptozotocin-induced diabetic rats. *International Journal of Nanomedicine, 10*, 6741-6756.

Baynes, J. W., & Thorpe, S. R. (1999). Role of oxidative stress in diabetes complications: A new perception on an old paradigm. *Diabetes, 48*(1), 1-9. http://dx.doi.org/10.2337/diabetes.48.1.1

Becker, D. J., Reul, B., Ozcelikay, A. T., Buchet, J. P., Henquin, J. C., & Brichard S. M. (1996). Oral selenate improves glucose homeostasis and partly reverses abnormal expression of liver glycolytic and gluconeogenic enzymes in diabetic rats. *Diabetologia, 39*(1), 3-11. http://dx.doi.org/10.1007/BF00400407

Bleys, J., Navas-Acien, A., & Guallar, E. (2007). Serum selenium and diabetes in U.S. adults. *Diabetes Care, 30*(4), 829-834. http://dx.doi.org/10.2337/dc06-1726

Burk, R. F. (2002). Selenium, an antioxidant nutrient. *Nutrition in Clinal Care, 5*(2), 75-79. http://dx.doi.org/10.1046/j.1523-5408.2002.00006.x

Chen, H., Qiu, Q., Zou, C., Dou, L., & Liang, J. (2015). Regulation of hepatic carbohydrate metabolism by Selenium during diabetes. *Chemico Biological Interactions, 232*, 1-6. http://dx.doi.org/10.1016/j.cbi.2015.02.017

Engelgau, M.M., Geiss, L.S., Saaddine, J.B., Boyle, J.P., Benjamin, S.M., Gregg, E.W., … Narayan, K.M. (2004). The evolving diabetes burden in the United States. *Annals of Internal Medicine, 140*(11), 945-950. http://dx.doi.org/10.7326/0003-4819-140-11-200406010-00035

Esteghamati, A., Gouya, M. M., Abbasi, M., Delavari, A., Alikhani, S., Alaedini, F., … Gregg, E.W. (2008). Prevalence of diabetes and impaired fasting glucose in the adult population of Iran: National Survey of Risk Factors for Non-Communicable Diseases of Iran. *Diabetes Care, 31*(1), 96-98. http://dx.doi.org/10.2337/dc07-0959

Farrokhian, A., Bahmani, F., Taghizadeh, M., Mirhashemi, S. M., Aarabi, M. H., Raygan, F., … Asemi, Z. (2016). Selenium Supplementation Affects Insulin Resistance and Serum hs-CRP in Patients with Type 2 Diabetes and Coronary Heart Disease. *Hormone and Metabolic Research, 48*(4), 263-268. http://dx.doi.org/10.1055/s-0035-1569276

Feng, W., Cui, X., Liu, B., Liu, C., Xiao, Y., Lu, W., … Wu, T. (2015). Association of urinary metal profiles with altered glucose levels and diabetes risk: a population-based study in China. *PLoS One, 10*(4), e0123742. http://dx.doi.org/10.1371/journal.pone.0123742

González de Vega, R., Fernández-Sánchez, M. L., Fernández, J. C., Álvarez Menéndez, F. V., & Sanz-Medel, A. (2016). Selenium levels and Glutathione peroxidase activity in the plasma of patients with type II diabetes mellitus. *Journal of Trace Elements in Medicine and Biology, 37*, 44-49. http://dx.doi.org/10.1016/j.jtemb.2016.06.007

Gouaref, I., Bellahsene, Z., Zekri, S., Alamir, B., & Koceir, E.A. (2016). The link between trace elements and metabolic syndrome/oxidative stress in essential hypertension with or without type 2 diabetes. *Annales de Biologie Clinique (Paris), 74*(2), 233-243.

Gurbanov, R., Bilgin, M., & Severcan, F. (2016). Restoring effect of selenium on the molecular content, structure and fluidity of diabetic rat kidney brush border cell membrane. *Biochimica et Biophysica Acta, 1858*(4), 845-854. http://dx.doi.org/10.1016/j.bbamem.2016.02.001

Hwang, D., Seo, S., Kim, Y., Kim, C., Shim, S., Jee, S., … Cho, J. (2007). 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. *Journal of Biosciences, 32*(4), 723-735. http://dx.doi.org/10.1007/s12038-007-0072-6

Kahya, M. C., Nazıroğlu, M., & Çiğ, B. (2015). Melatonin and selenium reduce plasma cytokine and brain oxidative stress levels in diabetic rats. *Brain Injury*, 1-7. [Epub ahead of print]

Kahya, M. C., Nazıroğlu, M., & Övey, İ. S. (2016). Modulation of Diabetes-Induced Oxidative Stress, Apoptosis, and Ca2+ Entry Through TRPM2 and TRPV1 Channels in Dorsal Root Ganglion and Hippocampus of Diabetic Rats by Melatonin and Selenium. *Molecular Neurobiology*, 2016 Mar 9. [Epub ahead of print] http://dx.doi.org/10.1007/s12035-016-9727-3

Kilinc, M., Guven, M. A., Ezer, M., Ertas, I. E., & Coskun, A. (2008). Evaluation of serum selenium levels in

Turkish women with gestational diabetes mellitus, glucose intolerants, and normal controls. *Biological Trace Element Research, 123*(1-3), 35-40. http://dx.doi.org/10.1007/s12011-007-8087-2

Kruse-Jarres, J. D., & Rukgauer, M. (2000). Trace elements in diabetes mellitus. Peculiarities and clinical validity of determinations in blood cells. *Journal of Trace elmenets in medicine and biology, 14*(1), 21-27.

Kumar, R. (2012). Correlation of Selenium and other antioxidants in diabetic patient with and without complications. *Free radicals and Antioxidants, 2*(1), 6-8. http://dx.doi.org/10.5530/ax.2012.2.3

Laclaustra, M., Navas-Acien, A., Stranges, S., Ordovas, J. M., & Guallar, E. (2009). Serum selenium concentrations and diabetes in U.S. adults: National Health and Nutrition Examination Survey (NHANES) 2003-2004. *Environmental Health Perspectives, 117*(9), 1409-1413. http://dx.doi.org/10.1289/ehp.0900704

Li, Y., Xu, W., Liao, Z., Yao, B., Chen, X., Huang, Z., … Weng, J. (2004). Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. *Diabetes Care, 27*(11), 2597-2602. http://dx.doi.org/10.2337/diacare.27.11.2597

Lu, C. W., Chang, H. H., Yang, K. C., Kuo, C. S., Lee, L. T., & Huang, K. C. (2016). High serum selenium levels are associated with increased risk for diabetes mellitus independent of central obesity and insulin resistance. *BMJ Open Diabetes Research & Care, 4*(1), e000253. http://dx.doi.org/10.1136/bmjdrc-2016-000253

Maritim, A. C., Sanders, R. A., & Watkins, J. B. (2003). Daibetes, Oxidative stress and Antioxidants: A review. *Journal of Biochemical and Molecular Toxicology, 17*(1), 24-38. http://dx.doi.org/10.1002/jbt.10058

Mueller, A. S., & Pallauf, J. (2006). Compendium of the antidiabetic effects of supranutritional selenate doses: in vivo and in vitro investigations with type II diabetic db/db mice. *The Journal of Nutritional Biochemistry, 17*(8), 548-560. http://dx.doi.org/10.1016/j.jnutbio.2005.10.006

Mueller, A. S., Mueller, K., Wolf, N. M., & Pallauf, J. (2009). Selenium and diabetes: An enigma? *FreeRadicalResearch, 43*(11), 1029-1059. http://dx.doi.org/10.1080/10715760903196925

Ogawa-Wong, A. N., Berry, M. J., & Seale, L. A. (2016). Selenium and Metabolic Disorders: An Emphasis on Type 2 Diabetes Risk. *Nutrients, 8*(2), 80. http://dx.doi.org/10.3390/nu8020080

Oztürk, Z., Gurpinar, T., Vural, K., Boyacıoglu, S., Korkmaz, M., & Var, A. (2015). Effects of selenium on endothelial dysfunction and metabolic profile in low dose streptozotocin induced diabetic rats fed a high fat diet. *Biotechnic & Histochemistry, 90*(7), 506-515. http://dx.doi.org/10.3109/10520295.2015.1042050

Rajpathak, S., Rimm, E., Morris, J.S., & Hu, F. (2005). Toenail selenium and cardiovascular disease in men with diabetes. *Journal of the American College of Nutrition, 24*(4), 250-256. http://dx.doi.org/10.1080/07315724.2005.10719472

Rayman, M. P. (2000). The importance of selenium to human health. *Lancet, 356*(9225), 233-241. http://dx.doi.org/10.1016/S0140-6736(00)02490-9

Rayman, M. P., & Stranges, S. (2013). Epidemiology of selenium and type 2 diabetes: Can we make sense of it? *Free Radical Biology and Medicine, 65*, 1557-1564. http://dx.doi.org/10.1016/j.freeradbiomed.2013.04.003

Robertson, R. P. (1995). Antagonist: diabetes and insulin resistance--philosophy, science, and the multiplier hypothesis. *The Journal of Laboratory and Clininical Medicine, 125*(5), 560-564.

Rotter, I., Kosik-Bogacka, D., Dołęgowska, B., Safranow, K., Lubkowska, A., & Laszczyńska, M. (2015). Relationship between the concentrations of heavy metals and bioelements in aging men with metabolic syndrome. *International Journal of Environmental Research and Public Health, 12*(4), 3944-3961. http://dx.doi.org/10.3390/ijerph120403944

Ruiz, C., alegria, A., Barbera, R., Farre, R., & Lagarda, M. J. (1998). Selenium, Zinc and Copper in Plasma of patients with Type 1 Diabetes Mellitus in Different Metabolic Control States. *Journal of Trace Elmenets in Medicine and Biology, 12*(2), 91-95. http://dx.doi.org/10.1016/S0946-672X(98)80031-X

Sailaja, Y.R., Baskar, R., & Saralakumari, D. (2003). The antioxidant status during maturation of reticulocytes to erythrocytes in type 2 diabetics. *Free Radical Biology & Medicine, 35*(2), 133-139. http://dx.doi.org/10.1016/S0891-5849(03)00071-6

Satyanarayana, S., Sekhar, J. R., Kumar, K. E., Shannika, L. B., Rajanna, B., & Rajanna, S. (2006). Influence of selenium (antioxidant) on gliclazide induced hypoglycaemia/anti hyperglycaemia in normal/alloxan-induced diabetic rats. *Molecular and Cellular Biochemistry, 283*(1-2), 123-127. http://dx.doi.org/10.1007/s11010-006-2387-2

Saxena, A. K. Srivastava, P., Kale, R. K., & Baquer, N. Z. (1993). Impaired Antioxidant status in diabetic rat liver. Effect of Vanadate. *Biochemical Pharmacology, 45*(3), 539-542. http://dx.doi.org/10.1016/0006-2952(93)90124-f

Sedighi, O., Makhlough, A., Shokrzadeh, M., & Hoorshad, S. (2014). Association between plasma selenium and glutathione peroxidase levels and severity of diabetic nephropathy in patients with type two diabetes mellitus. *Nephro-urology Monthly, 6*(5), e21355. http://dx.doi.org/10.5812/numonthly.21355

Steinbrenner, H., Speckmann, B., Pinto, A., & Sies, H. (2011). High selenium intake and increased diabetes risk: experimental evidence for interplay between selenium and carbohydrate metabolism. *Journal of Clinical Biochemistry and Nutrition, 48*(1), 40-45. http://dx.doi.org/10.3164/jcbn.11-002FR

Steinbrenner, H., Speckmann, B., & Klotz, L. O. (2016). Selenoproteins: Antioxidant selenoenzymes and beyond. *Archives of Biochemistry and Biophysics, 595*, 113-119. http://dx.doi.org/10.1016/j.abb.2015.06.024

Stranges, S., Marshall, J. R., Natarajan, R., Donahue, R. P., Trevisan, M., Combs, G. F., … Reid, M. E. (2007). Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Annals of Internal Medicine, 147*(4), 217-223. http://dx.doi.org/10.7326/0003-4819-147-4-200708210-00175

Stumvoll, M., Goldstein, B. J., & van Haeften, T. W. (2005). Type 2 diabetes: principles of pathogenesis and therapy. *Lancet, 365*(9467), 1333-1346. http://dx.doi.org/10.1016/S0140-6736(05)61032-X

Thompson, P. A., Ashbeck, E. L., Roe, D. J., Fales, L., Buckmeier, J., Wang, F., … Lance, P. (2016). Selenium Supplementation for Prevention of Colorectal Adenomas and Risk of Associated Type 2 Diabetes. *Journal of the National Cancer Institute, 108*(12), pii: djw152. http://dx.doi.org/10.1093/jnci/djw152

Thomson, C. D. (2004). Assessment of requirements for selenium and adequacy of selenium status: A review. *Europian Journal of Clinical Nutrition, 58*(3), 391-402. http://dx.doi.org/10.1038/sj.ejcn.1601800

Ubajaka, C. F., Meludu, S. C., Dioka, C. E., Onah, C. E., Osuji, C. U., Modebe, I. A.,… Nnebue, C. C. (2015). Evaluation of male sex hormones and trace elements in male type 2 diabetic patients attending NNAMDI AZIKIWE University teaching hospital diabetic clinics. *Nigerian Journal of Medicine, 24*(2), 162-168.

Wang, X. L., Yang, T. B., Wei, J., Lei, G. H., & Zeng, C. (2016). Association between serum selenium level and type 2 diabetes mellitus: a non-linear dose-response meta-analysis of observational studies. *Nutrition Journal, 15*(1), 48. http://dx.doi.org/10.1186/s12937-016-0169-6

Wang, X., Wu, H., Long, Z., Sun, Q., Liu, J., Liu, Y., & Hai, C. (2016). Differential effect of Se on insulin resistance: regulation of adipogenesis and lipolysis. *Molecular and Cellular Biochemistry, 415*(1-2), 89-102. http://dx.doi.org/10.1007/s11010-016-2679-0

Wei, J., Zeng, C., Gong, Q. Y., Yang, H. B., Li, X. X., Lei, G. H., & Yang, T. B. (2015). The association between dietary selenium intake and diabetes: a cross-sectional study among middle-aged and older adults. *Nutrition Journal, 14*, 18. http://dx.doi.org/10.1186/s12937-015-0007-2

Yadav, C., Manjrekar, P. A., Agarwal, A., Ahmad, A., Hegde, A., & Srikantiah, R. M. (2016). Association of Serum Selenium, Zinc and Magnesium Levels with Glycaemic Indices and Insulin Resistance in Pre-diabetes: a Cross-Sectional Study from South India. *Biological Trace Element Research*, 2016 Jun 6. [Epub ahead of print] http://dx.doi.org/10.1007/s12011-016-0766-4

Zou, C., Qiu, Q., Chen, H., Dou, L., & Liang, J. (2016). Hepatoprotective effects of selenium during diabetes in rats. *Human & Experimental Toxicology, 35*(2), 114-123. http://dx.doi.org/10.1177/0960327115579207

Copyrights