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MINIREVIEWS

Antioxidant role of zinc in diabetes mellitus

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Abstract

Chronic hyperglycemia statue noticed in diabetes mellitus favors the manifestation of oxidative stress by increasing the production of reactive oxygen species and/or by reducing the antioxidant defense system activity. Zinc plays an important role in antioxidant defense in type 2 diabetic patients by notably acting as a cofactor of the superoxide dismutase enzyme, by modulating the glutathione metabolism and metallothionein expression, by competing with iron and copper in the cell membrane and by inhibiting nicotinamide adenine dinucleotide phosphate-oxidase enzyme. Zinc also improves the oxidative stress in these patients by reducing chronic hyperglycemia. It indeed promotes phosphorylation of insulin receptors by enhancing transport of glucose into cells. However, several studies reveal changes in zinc metabolism in individuals with type 2 diabetes mellitus and controversies remain regarding the effect of zinc supplementation in the improvement of oxidative stress in these patients. Faced with the serious challenge of the metabolic disorders related to oxidative stress in diabetes along with the importance of antioxidant nutrients in the control of this disease, new studies may contribute to improve our understanding of the role played by zinc against oxidative stress and its connection with type 2 diabetes mellitus prognosis. This could serve as a prelude to the development of prevention strategies and treatment of disorders associated with this chronic disease.

Key words: Diabetes mellitus; Type 2; Oxidative stress; Zinc; Superoxide dismutase; Metabolism

Core tip: Type 2 diabetes mellitus is a metabolic disease characterized by the presence of chronic hyperglycemia which favors the manifestation of oxidative stress due to high production of reactive oxygen species and/or induced by the reduction of the antioxidant defense system activity. Zinc plays a relevant role in antioxidant defense in type 2 diabetic patients by acting through different protection mechanisms. Zinc for instance is an essential cofactor for superoxide dismutase enzyme. This mineral also facilitates reduction and neutralization of free radicals. The aim of the present review is to examine the antioxidant role of zinc in type 2 diabetic patients.

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INTRODUCTION

Type 2 diabetes mellitus is a metabolic disease characterized by the presence of glucose intolerance and hyperglycemia. The main pathophysiological effect is to induce a peripheral resistance to insulin action associated with a relative deficiency of secretion of this hormone in response to glucose[1,2].

Chronic hyperglycemia statue in diabetes favors the manifestation of oxidative stress due to high production of reactive oxygen species and/or a decrease of the antioxidant defense system activity linked to lipid peroxidation and oxidative cellular injury themselves resulting in damages in the metabolism of lipids, proteins and DNA and from changes in cells functions[3-5].

Hormonal, biochemical and nutritional disorders present in type 2 diabetic individuals have been subject to researches with the aim of clarifying the mechanisms involved in the pathogenesis of this disease. Regarding both biochemical and nutritional disorders, studies show changes in the mineral metabolism and the activity of antioxidant enzymes such as zinc and superoxide dismutase[6,7].

Zinc plays a relevant role in antioxidant defense in patients with type 2 diabetes mellitus. This mineral may act by different protection mechanisms by notably being an essential cofactor for more than 300 enzymes, such as superoxide dismutase. This mineral also facilitates reduction and neutralization of free radicals[8,9].

Considering changes in zinc metabolism and in superoxide dismutase enzyme activity present in type 2 diabetic patients simultaneously with the importance of these compounds in antioxidant defense, the aim of this review is to examine the antioxidant role of zinc in this type of patients.

RESEARCH

The bibliographical survey was conducted in the data base of Pubmed, Scielo and Lilacs, without limit of year of publication, considering the following inclusion criteria: studies that evaluated the effect of zinc supplementation on markers of oxidative stress in type 2 diabetes mellitus. Articles were selected for their originality and relevance, considering both the accuracy and adequacy of the experimental design, sample size, type of physiological and the performance measures undertaken. Classic and recent works were preferentially used.

The search of literature references was performed using the following keywords: "diabetes mellitus type 2", "zinc", "oxidative stress", "superoxide dismutase". The bibliographical survey included the following types of studies: randomized controlled clinical trials, cohort, case control study, being surveyed in 80 articles of which 36 were used, all of them related with this literature.

ZINC, OXIDATIVE STRESS AND TYPE 2 DIABETES MELLITUS

Recently, several researches have been conducted from the perspective of clarifying the connection between the metabolic and biochemical aspects involved in the pathogenesis of type 2 diabetes mellitus and the metabolism of minerals such as zinc. In this way, studies reveal changes in the metabolism of this nutrient and the results are still limited and controversial[6,10,11]. The Table 1 shows studies that evaluate participation of zinc in diabetes mellitus.

Saharia *et al*[6], Basaki *et al*[7] and Jansen *et al*[17] found reduced plasma concentration of zinc in type 2 diabetic patients. These results are associated with a high amount of the mineral lost in the urine. Such loss is influenced by glycemic control in these patients not compensated neither by an increase in its absorption by intestinal cells nor the concomitant reduction of intestinal excretion. Jayawardena[18] affirms that hyperglycemia interferes in active transport of zinc into the renal tubular cells promoting hyperzincuria.

Agte *et al*[10] found reduced zinc concentrations in the erythrocytes of type 2 diabetic patients compared to the control group, which seems to be related to the high osmotic fragility of erythrocytes resulting in oxidative stress. Percentage of hemolysis of theses cells also showed significant negative correlation with values of glycated hemoglobin.

On the other hand, study of Lima *et al*[11] found increased erythrocyte and plasma concentrations of zinc in type 2 diabetic patients compared to the control group. The authors suggest that plasma values observed are linked to the time of diagnosis of the disease, being higher at the beginning of its manifestation. About the erythrocyte concentration of the mineral, the authors have highlighted the role of metallothionein as a regulator of homeostasis of zinc. The oxidative stress present in type 2 diabetic patients indeed favors both the release of the mineral of this protein and the increase in intracellular zinc content.

Another factor that may favor the increase in zinc concentration in erythrocytes is the fact that oxidative damages induced by type 2 diabetes mellitus seem to be more prominent in erythrocytes, favoring increased concentration of antioxidants as a compensatory mechanism to protect these cells[11,19].

It is appropriate to draw attention to the antioxidant role of zinc. This mineral acts as a cofactor for superoxide dismutase enzyme, regulates the glutathione metabolism and the metallothionein expression, competes with iron and copper in the cell membrane and also inhibits the nicotinamide adenine dinucleotide phosphate-oxidase (NADPH-oxidase) enzyme[20,21].

Another important point is the action of a group of

Table 1 Studies that evaluate participation of zinc in diabetes mellitus

Ref.	Samples	Results
Aly *et al*[12]	Diabetics rats	Zinc chloride supplementation (5 mg/kg) during one month, helped maintain serum concentration of glucose; preserved hepatic tissue; diminished NO, MDA, and PEPCK and increased SOD, GSH, LDH, pyruvate kinase and hexokinase
Zhang *et al*[13]	Diabetics mice (n = 12) and control groups (n = 14)	Reduced hepatic zinc concentration were found in diabetics mice Zinc deficiency has contributed to increase serum concentrations of ALT and deposit of lipids in the liver of the mice. Furthermore, this deficiency stimulated expression of inflammatory cytokines PAI-1, TNF-α and ICAM-1 and the oxidative damage markers (3-NT e 4-HNE)
Gunasekara *et al*[14]	Diabetics adults: (n = 96) Group A (n = 29): Zinc and multivitamin/mineral complex supplementation Group B (n = 31): Multivitamin/mineral complex supplementation Group C (n = 36): Placebo	Zinc and multivitamin/mineral complex supplementation decreased serum concentrations of HbA1c, fasting glucose, postprandial glucose and serum cholesterol. This supplementation also decreased cholesterol/HDL ratio
Yoshikawa *et al*[15]	Diabetics mice (n = 8)	Bis(aspirinato)Zn complex supplementation improved glycemia, insulin resistance, leptin resistance, hypoadiponectinemia and arterial hypertension
Foster *et al*[16]	Women with type 2 diabetes mellitus (n = 48)	Zinc supplementation (40 mg/d) during 12 wk did not alter HbA1c, insulin and HOMA-IR values. Also, this supplementation did not change metallothionein and zinc transporters gene expression

ALT: Alanine aminotransferase; GSH: Reduced glutathione; HbA1c: Glycosylated haemoglobin; HDL: High-density lipoprotein; HOMA-IR: Homeostasis model of assessment–insulin resistance; LDH: Lactate dehydrogenase; MDA: Malondialdehyde; NO: Nitric oxide; PAI-1: Plasminogen activator inhibitor type 1; PEPCK: Phosphoenol pyruvate carboxykinase; SOD: Superoxide dismutase; TNF-α: Tumor necrosis factor-α; 3-NT: 3-nitrotyrosine; 4-HNE: 4-hydroxynonenal; ICAM-1: Intercellular adhesion molecule-1.

antioxidants enzymes called superoxide dismutase, which regulates the detoxification of reactive oxygen species and catalyzes the dismutation of superoxide anion into hydrogen peroxide and oxygen[22,23]. Mammals have three isoforms of this enzyme, but only isoforms 1 (CuZnSOD) and 3 (SOD extracelular) need zinc as a cofactor for its enzymatic activity and to act predominantly and respectively in the intracellular space and extracellular fluids[20,24,25].

A study by Zhu *et al*[22] with diabetic mice shows that the zinc supplementation increased the activity of superoxide dismutase and reduced malondialdehyde concentrations in both serum and pancreas. According to the authors, low levels of zinc in the organism impair the action of the antioxidant defense system. Corroborating previous findings, Li *et al*[3] verified that zinc supplementation increased the activity of superoxide dismutase and decreased lipid peroxidation in the liver of diabetic rats, emphasizing that zinc can protect the liver from oxidative damage.

However, Anderson *et al*[26] did not find any increase in superoxide dismutase activity after supplementation with 30 mg of zinc for 6 mo in type 2 diabetic patients. Roussel *et al*[27] supplemented type 2 diabetic patients with 30 mg of zinc gluconate over 6 mo and noticed a reduction in the production of reactive substances to the thiobarbituric acid, but did not find any increase in the activity of superóxido dismutase.

Action of zinc on glutathione metabolism is significant and as such must be mentioned. Zinc indeed influences the expression of glutamate-cysteine ligase enzyme involved in the synthesis of glutathione, which directly acts on the neutralization of free radicals and indirectly as a cofactor of glutathione peroxidase[20,28].

Karatug *et al*[29] performed zinc sulfate supplementation in diabetic rats and found both an increased concentration of glutathione and a diminution of the lipid peroxidation. The non-enzymatic glycosylation in renal tissue substantiate the relevant antioxidant properties of this mineral in reducing the risk of renal complications associated with type 2 diabetes mellitus.

In terms of zinc action on metallothionein expression, numerous studies indicate that zinc supplementation increases both mRNA levels and the activity of such enzyme in type 2 diabetic individuals. The induction of metalloprotein being one of the explanations for the protective effect of supplementation with zinc in these patients[30,31].

Wang *et al*[32] evaluated the effects of zinc supplementation in diabetic rats and found reduced concentrations of blood glucose and malondialdehyde, as well as an increased expression of metallothionein in the liver. No changes in serum zinc levels were observed, implying a beneficial effect of supplementation in the reduction of oxidative stress.

A study by Özcelik *et al*[31] showed that zinc supplementation increased the concentrations of both metallothionein and zinc, and decreased the lipid peroxidation in renal tissue of diabetic rats, showing the performance of the mineral acting as an antioxidant nutrient and its role in the prevention of renal damages in type 2 diabetes mellitus.

On the other hand, Seet *et al*[33] evaluated the effect of an intake of 240 mg zinc/d in type 2 diabetic

patients with normozincemia and observed that the supplementation with this nutrient did not change the concentration of markers of oxidative stress and vascular function, suggesting that high doses of zinc have no beneficial effect on diabetics who do not have hypozincemia.

Another mechanism that explains the antioxidant role of zinc in type 2 diabetes mellitus, refers to its ability to compete with iron and copper for binding sites on the cell membrane. The iron and copper ions can catalyze the production of lipid peroxides, and the replacement of these metals for zinc in the plasma membrane could prevent lipid peroxidation in diabetic patients[28].

The literature has shown that zinc also regulates the production of free radicals in neuronal cells in type 2 diabetic individuals. This mineral is known for its inhibiting effect on N-methyl-D-aspartate (NMDA) receptors involved in calcium transportation from the extracellular medium to the cytosol. Therefore, in case of zinc deficiency, NMDA receptors activation promotes and increase intracellular calcium concentration. In return, NADPH-oxidase and nitric oxide synthase enzymes are activated, favoring the production of reactive oxygen and nitrogen species[28].

Liu *et al*[34] noticed that zinc supplementation decreased malondialdehyde concentration and stimulated the transcription of metallothionein genes in peripheral nerves of diabetic mice. This suggests that this mineral may improve peripheral neuropathy associated with type 2 diabetes. Such protective effect seems to be mediated by the reduction of oxidative stress.

Zhu *et al*[22] observed that zinc supplementation in diabetic rats caused an increase in glutathione peroxidase enzyme activity as well as a drop in concentrations of malondialdehyde and nitric oxide. The nitric oxide synthase activity in both pancreas and serum of these rats also demonstrates the protective action of zinc against oxidative stress present in type 2 diabetes mellitus. Moreover, the authors observed that the intake of this mineral improved liver functions and also prevent damage to pancreatic tissue induced by the diabetes.

Oxidative stress found in type 2 diabetes is improved by the action of zinc because it also reduces chronic hyperglycemia. It is important to point out that this oligoelement takes part in insulin inventory, secretion and action processes for being a catalytic cofactor for carboxypeptidase H enzyme which catalyzes the conversion from proinsulin (inactive) into insulin (active). Zinc also promotes phosphorylation of insulin receptor by enhancing glucose transport into cells[30,35]. In this perspective, Vashum *et al*[36] demonstrated the role of zinc in reducing chronic hyperglycemia in type 2 diabetes mellitus by considering that patients with higher serum concentration of the mineral improved their insulin sensitivity.

Considering the biochemical and nutritional aspects presents in type 2 diabetes mellitus pathophysiology, important is the participation of zinc in mechanisms involved in this process, for instance, its relevant role as an antioxidant nutrient that improve metabolic control in these patients.

CONCLUSION

Scientific evidences highlighted in this review point out changes in zinc metabolism which contributes to an oxidative stress manifestation in patients with type 2 diabetes mellitus. Several researches have found controversial results regarding zinc supplementation and its positive impact on oxidative stress in these patients. Faced with the serious challenge of the metabolic disorders related to oxidative stress in diabetes in addition to the importance of antioxidant nutrients in the control of this disease, the carrying out of studies may contribute to improve our understanding of the role played by zinc against oxidative stress and its connection with type 2 diabetes mellitus prognosis. This could serve as a prelude to the development of prevention strategies and treatments of disorders associated with this chronic disease.

REFERENCES

1 **American Diabetes Association**. Standards of medical care in diabetes--2012. *Diabetes Care* 2012; **35** Suppl 1: S11-S63 [PMID: 22187469 DOI: 10.2337/dc12-5011]

2 **Ramakrishna V**, Jailkhani R. Oxidative stress in non-insulin-dependent diabetes mellitus (NIDDM) patients. *Acta Diabetol* 2008; **45**: 41-46 [PMID: 17924055 DOI: 10.1007/s00592-007-0018-3]

3 **Li Y**, Jaddoe VW, Qi L, He Y, Wang D, Lai J, Zhang J, Fu P, Yang X, Hu FB. Exposure to the chinese famine in early life and the risk of metabolic syndrome in adulthood. *Diabetes Care* 2011; **34**: 1014-1018 [PMID: 21310886 DOI: 10.2337/dc10-2039]

4 **Pan HZ**, Zhang L, Guo MY, Sui H, Li H, Wu WH, Qu NQ, Liang MH, Chang D. The oxidative stress status in diabetes mellitus and diabetic nephropathy. *Acta Diabetol* 2010; **47** Suppl 1: 71-76 [PMID: 19475334 DOI: 10.1007/s00592-009-0128-1]

5 **Shams ME**, Al-Gayyar MM, Barakat EA. Type 2 Diabetes Mellitus-Induced Hyperglycemia in Patients with NAFLD and Normal LFTs: Relationship to Lipid Profile, Oxidative Stress and Pro-Inflammatory Cytokines. *Sci Pharm* 2011; **79**: 623-634 [PMID: 21886908 DOI: 10.3797/scipharm.1104-21]

6 **Saharia GK**, Goswami RK. Evaluation of serum zinc status and glycated hemoglobin of type 2 diabetes mellitus patients in a tertiary care hospital of assam. *J Lab Physicians* 2013; **5**: 30-33 [PMID: 24014965 DOI: 10.4103/0974-2727.115923]

7 **Basaki M**, Saeb M, Nazifi S, Shamsaei HA. Zinc, copper, iron, and chromium concentrations in young patients with type 2 diabetes mellitus. *Biol Trace Elem Res* 2012; **148**: 161-164 [PMID: 22351156]

8 **Prasad AS**. Zinc in human health: effect of zinc on immune cells. *Mol Med* 2008; **14**: 353-357 [PMID: 18385818 DOI: 10.2119/2008-00033]

9 **Carocho M**, Ferreira IC. A review on antioxidants, prooxidants and related controversy: natural and synthetic compounds, screening and analysis methodologies and future perspectives. *Food Chem Toxicol* 2013; **51**: 15-25 [PMID: 23017782 DOI: 10.1016/j.fct.2012.09.021]

10 **Agte VV**, Nagmote RV, Tarwadi KV. Comparative in vitro uptake of zinc by erythrocytes of normal vs Type 2 diabetic individuals and the associated factors. *Diabetes Nutr Metab* 2004; **17**: 343-349 [PMID: 15887628]

11 **Lima VB**, Sampaio Fde A, Bezerra DL, Moita Neto JM, Marreiro Ddo N. Parameters of glycemic control and their relationship with zinc concentrations in blood and with superoxide dismutase

enzyme activity in type 2 diabetes patients. *Arq Bras Endocrinol Metabol* 2011; **55**: 701-707 [PMID: 22231973 DOI: 10.1590/S0004-27302011000900006]
12 **Aly HF**, Mantawy MM. Comparative effects of zinc, selenium and vitamin E or their combination on carbohydrate metabolizing enzymes and oxidative stress in streptozotocin induced-diabetic rats. *Eur Rev Med Pharmacol Sci* 2012; **16**: 66-78 [PMID: 22338550]
13 **Zhang C**, Lu X, Tan Y, Li B, Miao X, Jin L, Shi X, Zhang X, Miao L, Li X, Cai L. Diabetes-induced hepatic pathogenic damage, inflammation, oxidative stress, and insulin resistance was exacerbated in zinc deficient mouse model. *PLoS One* 2012; **7**: e49257 [PMID: 23251339 DOI: 10.1371/journal.pone.0049257]
14 **Gunasekara P**, Hettiarachchi M, Liyanage C, Lekamwasam S. Effects of zinc and multimineral vitamin supplementation on glycemic and lipid control in adult diabetes. *Diabetes Metab Syndr Obes* 2011; **4**: 53-60 [PMID: 21448322 DOI: 10.2147/DMSO.S16691]
15 **Yoshikawa Y**, Adachi Y, Yasui H, Hattori M, Sakurai H. Oral administration of Bis(aspirinato)zinc(II) complex ameliorates hyperglycemia and metabolic syndrome-like disorders in spontaneously diabetic KK-A(y) mice: structure-activity relationship on zinc-salicylate complexes. *Chem Pharm Bull* (Tokyo) 2011; **59**: 972-977 [PMID: 21804241 DOI: 10.1248/cpb.59.972]
16 **Foster M**, Chu A, Petocz P, Samman S. Zinc transporter gene expression and glycemic control in post-menopausal women with Type 2 diabetes mellitus. *J Trace Elem Med Biol* 2014; **28**: 448-452 [PMID: 25156968 DOI: 10.1016/j.jtemb.2014.07.012]
17 **Jansen J**, Rosenkranz E, Overbeck S, Warmuth S, Mocchegiani E, Giacconi R, Weiskirchen R, Karges W, Rink L. Disturbed zinc homeostasis in diabetic patients by in vitro and in vivo analysis of insulinomimetic activity of zinc. *J Nutr Biochem* 2012; **23**: 1458-1466 [PMID: 22402369 DOI: 10.1016/j.jnutbio.2011.09.008]
18 **Jayawardena R**, Ranasinghe P, Galappatthy P, Malkanthi R, Constantine G, Katulanda P. Effects of zinc supplementation on diabetes mellitus: a systematic review and meta-analysis. *Diabetol Metab Syndr* 2012; **4**: 13 [PMID: 22515411 DOI: 10.1186/1758-5996-4-13]
19 **Cimbaljević B**, Vasilijević A, Cimbaljević S, Buzadzić B, Korać A, Petrović V, Janković A, Korać B. Interrelationship of antioxidative status, lipid peroxidation, and lipid profile in insulin-dependent and non-insulin-dependent diabetic patients. *Can J Physiol Pharmacol* 2007; **85**: 997-1003 [PMID: 18066100 DOI: 10.1139/Y07-088]
20 **Foster M**, Samman S. Zinc and redox signaling: perturbations associated with cardiovascular disease and diabetes mellitus. *Antioxid Redox Signal* 2010; **13**: 1549-1573 [PMID: 20568953 DOI: 10.1089/ars.2010.3111]
21 **Ruz M**, Carrasco F, Rojas P, Codoceo J, Inostroza J, Basfi-fer K, Valencia A, Vásquez K, Galgani J, Pérez A, López G, Arredondo M, Perez-Bravo F. Zinc as a potential coadjuvant in therapy for type 2 diabetes. *Food Nutr Bull* 2013; **34**: 215-221 [PMID: 23964394]
22 **Zhu K**, Nie S, Li C, Huang J, Hu X, Li W, Gong D, Xie M. Antidiabetic and pancreas-protective effects of zinc threoninate chelate in diabetic rats may be associated with its antioxidative stress ability. *Biol Trace Elem Res* 2013; **153**: 291-298 [PMID: 23625696]
23 **Arif M**, Islam MR, Waise TM, Hassan F, Mondal SI, Kabir Y. DNA damage and plasma antioxidant indices in Bangladeshi type 2 diabetic patients. *Diabetes Metab* 2010; **36**: 51-57 [PMID: 20036596 DOI: 10.1016/j.diabet.2009.05.007]
24 **Di Naso FC**, Simões Dias A, Porawski M, Marroni NA. Exogenous superoxide dismutase: action on liver oxidative stress in animals with streptozotocin-induced diabetes. *Exp Diabetes Res* 2011; **2011**: 754132 [PMID: 21437212 DOI: 10.1155/2011/754132]
25 **Kurinenko BM**, Kashkin AP, Kalacheva NV, Meringova LV, Nekhoroshkova ZM. [Structural and antigenic differences of pancreatic RNAse preparations modified by dextran ethers in an azo-combination reaction]. *Biokhimiia* 1985; **50**: 581-588 [PMID: 2408680 DOI: 10.5999/aps.2013.40.5.517]
26 **Anderson RA**, Roussel AM, Zouari N, Mahjoub S, Matheau JM, Kerkeni A. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. *J Am Coll Nutr* 2001; **20**: 212-218 [PMID: 11444416 DOI: 10.1080/07315724.2001.10719034]
27 **Roussel AM**, Kerkeni A, Zouari N, Mahjoub S, Matheau JM, Anderson RA. Antioxidant effects of zinc supplementation in Tunisians with type 2 diabetes mellitus. *J Am Coll Nutr* 2003; **22**: 316-321 [PMID: 12897047 DOI: 10.1080/07315724.2003.10719310]
28 **Oteiza PI**. Zinc and the modulation of redox homeostasis. *Free Radic Biol Med* 2012; **53**: 1748-1759 [PMID: 22960578 DOI: 10.1016/j.freeradbiomed.2012.08.568]
29 **Karatug A**, Kaptan E, Bolkent S, Mutlu O, Yanardag R. Alterations in kidney tissue following zinc supplementation to STZ-induced diabetic rats. *J Trace Elem Med Biol* 2013; **27**: 52-57 [PMID: 22944585 DOI: 10.1016/j.jtemb.2012.07.006]
30 **Miao X**, Sun W, Fu Y, Miao L, Cai L. Zinc homeostasis in the metabolic syndrome and diabetes. *Front Med* 2013; **7**: 31-52 [PMID: 23385610 DOI: 10.1007/s11684-013-0251-9]
31 **Özcelik D**, Nazıroglu M, Tunçdemir M, Çelik Ö, Öztürk M, Flores-Arce MF. Zinc supplementation attenuates metallothionein and oxidative stress changes in kidney of streptozotocin-induced diabetic rats. *Biol Trace Elem Res* 2012; **150**: 342-349 [PMID: 23054862]
32 **Wang X**, Li H, Fan Z, Liu Y. Effect of zinc supplementation on type 2 diabetes parameters and liver metallothionein expressions in Wistar rats. *J Physiol Biochem* 2012; **68**: 563-572 [PMID: 22585619]
33 **Seet RC**, Lee CY, Lim EC, Quek AM, Huang H, Huang SH, Looi WF, Long LH, Halliwell B. Oral zinc supplementation does not improve oxidative stress or vascular function in patients with type 2 diabetes with normal zinc levels. *Atherosclerosis* 2011; **219**: 231-239 [PMID: 21840002 DOI: 10.1016/j.atherosclerosis.2011.07.097]
34 **Liu F**, Ma F, Kong G, Wu K, Deng Z, Wang H. Zinc supplementation alleviates diabetic peripheral neuropathy by inhibiting oxidative stress and upregulating metallothionein in peripheral nerves of diabetic rats. *Biol Trace Elem Res* 2014; **158**: 211-218 [PMID: 24615552]
35 **Capdor J**, Foster M, Petocz P, Samman S. Zinc and glycemic control: a meta-analysis of randomised placebo controlled supplementation trials in humans. *J Trace Elem Med Biol* 2013; **27**: 137-142 [PMID: 23137858 DOI: 10.1016/j.jtemb.2012.08.001]
36 **Vashum KP**, McEvoy M, Milton AH, Islam MR, Hancock S, Attia J. Is serum zinc associated with pancreatic beta cell function and insulin sensitivity in pre-diabetic and normal individuals? Findings from the Hunter Community Study. *PLoS One* 2014; **9**: e83944 [PMID: 24416185 DOI: 10.1371/journal.pone.0083944]

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