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

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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 a cofactor of 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.

Cruz KJC, Oliveira ARS, Marreiro DN. Antioxidant role of zinc in diabetes mellitus. World J Diabetes 2015; 6(2): 333-337
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[6,9].

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[11,10].

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
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. Mammals have three isoforms of this enzyme, but only isoforms 1 (CuZnSOD) and 3 (SOD extracellular) need zinc as a cofactor for its enzymatic activity and to act predominantly and respectively in the intracellular space and extracellular fluids.

A study by Zhu et al. 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. 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. 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. 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 superoxide 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.

Karatug et al. 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.

Wang et al. 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. 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. evaluated the effect of an intake of 240 mg zinc/d in type 2 diabetic

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 (TGF-β, 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.
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\(^\text{[28]}\).

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\(^\text{[28]}\).

Liu et al\(^\text{[30]}\) 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\(^\text{[22]}\) 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 prevented 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\(^\text{[20,25]}\).

In this perspective, Vashum et al\(^\text{[28]}\) 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.

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