Chapter 6

# Trace Elements Modulates Oxidative Stress in Type 2 Diabetes

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**Abstract**

The relationship between antioxidant trace elements (ATE) and metabolic disease is subtle and complex due to overproduction of reactive oxygen species (ROS). In type 2 diabetes (T2D), the relationship between ATE and insulin-like trace elements is very complex during oxidative stress (OS), being mediated by hyperglycemia, dyslipidemia and inflammation. The important role assigned to ATE (zinc, selenium, copper, manganese and chromium) by their involvement at different levels: Hemodynamic homeostasis (endothelial function and protein glycation), energy metabolism (carbohydrate and lipid tolerance) and enzymatic antioxidant protection [superoxide dismutase (SOD), glutathione peroxidase (GPx)]. The ROS-mediated cellular signaling process is crucial. Manganese and selenium levels abnormalities might to be useful indicators of oxidative damage. Two major factors were suggested: lack of Mn bioavailability leading to the decrease of mitochondrial SOD activity (cytosolic SOD remains active), and low blood selenium level implying a decrease in GPx activity. In T2D pathophysiology, it appears that antioxidant defense is preserved in the cytosol (Cu/Zn-SOD) in T2D, whereas it is impaired in mitochondria (Mn-SOD) in the three pathologies, which make this cell organelle a true ATE therapeutic target. Future challenges require the in-depth investigations of mitochondrial mechanisms, involved the antioxidant trace elements signaling pathways in T2D pathophysiology.

**Keywords:** type 2 diabetes, oxidative stress, antioxidant trace elements (zinc, selenium, copper, manganese, and chromium)

## 1. Introduction

Type 2 diabetes (T2D) is a major risk factor for cardiovascular diseases and acute oxidative stress (OS) by high production of reactive oxygen species (ROS) related to the lipotoxicity and glucotoxicity processes [1]. The mechanisms underlying OS disorders modulated by antioxidant trace

elements (ATE) such as selenium (Se), manganese (Mn), zinc (Zn), copper (Cu) and chromium (Cr) status are not completely clear [2]. The role of ATE as an essential micronutrient has been identified for a long time as a potential candidate for improving metabolic disorders, like glucose homeostasis in prediabetes state [3]. Antioxidant enzymatic system (AES) such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase plays an important protective role in the emergency of glucose intolerance, insulin resistance and dyslipidemia. T2D is characterized by elevated glycated hemoglobin (HbA1c) and insulin resistance maintains the toxic hyperglycemia and dyslipidemia effects, leads to disturb ATE status. This situation amplifies OS and aggravates the diabetes vascular complications [4].

The ROS neutralization is conducted primarily by AES through ATE integrated as AES cofactors. Cu and Zn are incorporated both into the Cu-Zn-SOD to reduce the cytotoxic ROS effects in cytosolic compartment cells [5]. Mn is incorporated into the Mn-SOD to remove the ROS effects in mitochondrial compartment cells [6]. Se is incorporated into the GPx1 to remove the ROS effects in cytosolic and mitochondrial compartment cells [7]. The present review updates our actual state of knowledge about highlight role of ATE in OS damage in T2D pathogenesis, and that consider their therapeutic potential.

Several studies have reported that pathogenesis of type 2 diabetes (T2D) is related to the imbalance of some antioxidant trace elements such as zinc, selenium, copper, manganese and chromium might adversely affect pancreatic islet and cause development of diabetes [8]. Type 2 diabetes is clearly associated with ROS production and insulin signaling depends on the balance of ROS production and antioxidant defense. Excessive ROS are involved in the multifactorial etiology of insulin resistance and the subsequent development of T2D [9]. Oxidative stress alters the insulin receptor and the insulin receptor substrate (IRS) signaling pathway via kinase activity (serine/threonine), leading to multi-site phosphorylation [10]. These events increase serine IRS phosphorylation and decrease thyrosine, leading to insulin resistance [11]. The ATE trace elements shows a profile disturbance in T2D is associated with increased proinflammatory cytokines (TNF-$\alpha$, IL-6) may contribute to development of diabetic complications [12, 13] and increased glycated hemoglobin formation [4].

## 2. Zinc in T2D pathogenesis

Zinc (Zn) is a necessary micronutrient which has an essential role in insulin metabolism [14, 15]. In pancreatic beta cells, Zn is required for the synthesis, storage and insulin secretion [79]. It has been described in diabetic subjects pancreas is zinc deficiency compared to normal subject. These data confirmed that zinc is involved in insulin signaling pathways [16]. Zn may stimulate energy consumption in skeletal muscle and brown adipose tissue and may increase the pancreatic insulin content and improve the glucose tolerance test [17]. Zn is found largely in cereals, animal protein and seafood [18]. Zn absorption can be inhibited by iron. Zn is transported across cell membranes via ZnT family's transporters [19].

In diabetes diseases (insulin resistance, metabolic syndrome), Zn is considered important mainly because: (i) it plays a major role in the stabilization of insulin hexamers and the hormone pancreatic storage [20] and (ii) it is an efficient antioxidant [21]. Zinc deficiency in

type 2 diabetes is mainly due to a significant urinary zinc loss [22], nevertheless, this Zinc deficiency is not very significant versus healthy subject [23]. Lower Zn plasma concentrations were found in T2D to relate of cardiovascular risk metabolic syndrome factors [24], and reduced Zn levels in diabetics appear to be related to increased risk for coronary artery disease [25]. It has been described that zinc effects mimic the insulin action mainly via the glycogen synthesis/degradation enzymes signaling pathways [26]. Other mechanisms include Cu/Zn-superoxide dismutase regulation via the post receptor proteins Akt and PI3-kinase via NF_B [27]. On the other hand, some particular forms of Zn have been discovered in ob/ob mice, such Zn-$\alpha$ 2-glycoprotein is an adipokine which stimulates energy expenditure in skeletal muscle and brown adipose tissue, resulting in reductions in glycaemia, triglycerides and Free Fatty Acids. Their level is lower in obese human subcutaneous and visceral adipose tissue and liver, but interestingly does not appear to be related to insulin resistance [28].

## 3. Selenium in T2D pathogenesis

Early studies indicated that inorganic Se acted as an insulin mimic [29] and epidemiologic investigations showed correlations between abnormal glucose or lipid metabolism and decreased plasma Se concentrations or glutathione peroxidase activity in diabetic subjects [30–32]. Indeed, intraperitoneal injection or oral administration of sodium selenate improved glucose homeostasis in type 1 and type 2 diabetic animals [33]. Similarly, previous studies have shown that the insulin-like and antidiabetic effects of sodium selenite and selenomethionine were also observed in diabetic animals [34]. Several selenium supplementation studies were undertaken in diabetic subject with vascular complications, unfortunately the beneficial antioxidant effects were not obtained [35, 36].

Se is a key component of GPx, an enzyme that prevents the cells oxidation. Compared with liver, islets contain only 2% GPx [37]. Accordingly, $\beta$ cells are considered to be low in antioxidant defenses and susceptible to oxidative stress. In diabetic subjects, $\beta$-cell apoptosis seems to be more of a deciding factor than replication in controlling the cell mass compared with control subjects [38]. Selenoprotein (SelP), a secretory protein primarily produced by the liver and regulated similar to that of the gluconeogenic enzyme glucose 6-phosphatase [39], by concerted action of peroxisome proliferator-activated receptor co activator 1$\alpha$ (PPAR-1$\alpha$) and the transcription hepatocyte nuclear factor-4$\alpha$ [40]. It has been shown a positive correlation between hepatic SelP mRNA levels and insulin resistance in humans, a long with a positive correlation between serum SelP levels and both fasting plasma glucose and hemoglobin A1C (HbA1c) levels. The metabolic selenium effects are mediated by selenoproteins (SeP) via the adenosine monophosphate-activated protein kinase (AMPK) inactivation [41]. Probably, SePs insulin-sensitizing effect like to glutathione peroxidase (GPx). However, SelP does not seem to act upon insulin synthesis or a trophic effect on pancreatic beta mass cells [42].

On the other hand, some studies have shown that Tanis (in humans encoded by the SelP gene) was regulated by glucose and altered in the diabetic state [43]. It has been reported that Tanis protein overexpression in H4IIE cells acts at different points: (i) glucose transport; (ii) basal insulin secretion; (iii) glycogen synthesis and storage; (iv) attenuates the phosphoenol pyruvate

carboxykinase gene expression [44]. These data confirm that Tanis protein is involved in glycemic homeostasis and hepatic insulin resistance. Furthermore, emerging evidence suggests that elevation of SelP [45] mRNA and protein expression was observed in T2D patients. Otherwise, it has been described that Selenium modulates vascular inflammatory syndrome by reducing p38 MAP kinase and NF-κB signaling pathway [46]. Besides, selenium is able to inhibit atherosclerotic processes by endothelial adhesion molecules expression [47].

## 4. Copper in T2D pathogenesis

Plasma Cu concentrations have been reported in some studies to be altered in diabetic humans compared to non-diabetics [4], particularly in diabetic patients with microvascular disease complications [48] and proteinuria [49]. Similarly, serum ceruloplasmin has been noted to be higher in T2D subjects compared to non-diabetics in numerous studies [50]. Alterations in Cu metabolism coupled with an increase in glycated proteins [4] may contribute to the progression of diabetes-related pathologies. Several lines of evidence support a role of Cu in diabetes-induced oxidative stress. Several previous studies have showed that ceruloplasmin can be fragmented following non-enzymatic glycosylation [51]. Secondly, glycation of CuZn-SOD in humans with diabetes leads to a site-specific fragmentation resulting in its inactivation [52] as well as the release of Cu, which can further exacerbate oxidative stress. Glycation of CuZn-SOD increases the formation of DNA damage in vitro, which suggests that the release of $Cu^{2+}$ from glycated SOD can participate in cleavage of nuclear DNA [53]. As CuZn-SOD accounts for 90% of the total SOD activity of the mouse lens [54], the excessively high concentrations of glycated CuZn-SOD in diabetic rat lenses are postulated to be involved in lens pathology [55]. Cu can increase the rate advanced glycated end (AGE) products formation, which is associated with the pathogenesis of secondary complications in diabetes [56]. Agents used to prevent or reduce AGE formation typically have potent Cu chelating [57].

## 5. Manganese in T2D pathogenesis

The manganese status in T2D is still unclear and the few studies that have addressed this issue in humans are controversial. However, Mn acts as a cofactor in several metalloenzymes including those involved in glucose homeostasis (*Pyruvate carboxylase, GTP oxaloacetate carboxylase, Isocitrate dehydrogenase, Malate dehydrogenase, Phosphoenolpyruvate carboxykinase*). These enzymes play a critical role in the blood glucose regulation via glycolysis, gluconeogenesis, Krebs cycle [58]. Mn is required for insulin synthesis [59], and to regulate of glucose utilization and lipogenesis in adipose tissue [60]. Previous studies have shown that blood manganese levels are unchanged in plasma, not significantly (approx. 15%) reduced in whole blood [61], or decreased in erythrocytes [62], from diabetic patients as compared to controls. In healthy subjects, manganese is very present in tissues rich in mitochondria (12–16 mg), in particular skeletal muscle, liver, pancreas and kidney. Mn is necessary for the synthesis, secretion and action of insulin. Mn is also indispensable for the maturation of bones and cartilage. Mn plasma levels are essentially regulated via the bile excretion pathway. Mn also

participates in vitamins E and B1 synthesis [63]. Mn is found mainly in quinoa, rye, whole rice, soybeans, avocado, egg yolk, green beans, spinach, walnuts, olive oil, oysters, green tea and provence herbs [64].

Our recently diabetes investigation [65], we found Mn blood concentrations are significantly increased (23%) in diabetic patients compared to controls. The correlation is positive with hyperglycemia and HbA1C. Our data suggest that Mn play a crucial role in antioxidant capacity and we hypothesize that antioxidant defense is preserved in the cytosol (superoxide dismutase Cu/Zn-SOD), whereas it is impaired in mitochondria (Mn-SOD), which makes this cell organelle a true therapeutic target in diabetes. In our recent study, we showed the competitive effect between the manganese and iron in T2D. However, when the iron was in the free form and reduced, it was constantly a pro-oxidant, whereas Mn was an anti-oxidant. Several studies suggesting that transferrin (Tf)/Tf receptor (TfR) transport system is the major transport of manganese and iron in plasma. The Mn bioavailability is reduced due to altered Tf/TfR transport system [66–69]. Consequently, the Mn (III) forms a more stable with Tf than the Mn (II) form [70]. The more complex questions related to the regulation of each by Mn and Fe might affect the insulin secretion and glucose homeostasis. Probably the increased Mn levels would affect the availability or concentration of both various transporters and finally bêta cell Mn distribution [71]. The interactions of Mn, Fe and ferritin are closely related in the following manner; and can lead to hyperglycemia associated to mitochondrial Fe, Mn, copper, and zinc levels [72], demonstrating the interrelationship with glycemia homeostasis. Probably, that the heightened β-cell oxidative stress may result from occurring Tf/Tf receptor system, and elevated manganese is produced via an extracellular Tf-manganese redox mechanism, rather than simply the presence of elevated tissue manganese per se. In this context, the plasma manganese accumulation was associated to iron plasma depletion and ferritin increased, suggesting that mitochondrial iron accumulation resulting in generation of ROS by Fenton chemistry [73]. The Mn is confined to the cytosol where it is associated with decreased mitochondrial SOD-Mn due the lack of mitochondrial manganese. The finding that DT2 pathogenesis are able to regulate manganese transport into, and/or export from, mitochondria and maintain a normal pool of mitochondrial manganese, despite the presence of a two-fold increase in cytosolic manganese content. Among possible explanations for this result, the upregulation of mitochondrial manganese transporters in situations of large changes in metal availability, or a heretofore undescribed function for the transferrin in regulation of mitochondrial metal accumulation. At last, in diabetes vascular complications, Mn is involved in Arginine production, precursor to nitric oxide (NO) formation as endothelial vasodilator [74].

## 6. Chromium in T2D pathogenesis

Chromium (Cr) that is mineral trace deserves special attention in diabetes pathophysiology, as has been reported during the 50th anniversary of this trace element and they termed it glucose tolerance factor (GTF) [75]. The Cr recommended nutritional requirements are estimated between 50 and 200 mg, but this requirement is estimated at 30 mg/day. Barley is the most important Cr food source [76]. Cr plays a crucial role in glycaemia homeostasis and Cr deficiency leads to a glucose tolerance disorder, moderate fasting hyperglycemia and occasionally

dyslipidemia. This observation has been observed both in human clinical and experimental models [77, 78]. Cr plasma concentrations can be explained by its mobilization from its storage site (liver, kidneys) to the blood by chromodulin binding (intracellular transport protein) [79]. However, Cr bioavailability depends on the nutrients with which it is associated: Cr/phenylalanine, Cr/cysteine, Cr/biotin and Cr/vitamin E or Cr/vitamin C complexes have been described [80–83]. Cr acts as carbohydrate tolerance factor, increases insulin sensitivity, particularly in the skeletal muscle. Indeed, trivalent chromium is an insulin pathway signaling. Cr increases insulin receptors number, insulin internalization and an activation of the GLUT4 and GLUT1 glucose carriers translocation [84]. The insulin binding to the $\alpha$-subunit receptor is induced by a phosphorylation reactions cascade catalyzed by tyrosine kinase that is activated by Cr; however, phosphotyrosine phosphatase which inactivates the insulin receptor is inhibited by Cr [85]. In type 2 diabetes and obesity, the Cr deficiency can be observed in subjects consuming excessively rapid absorption carbohydrates that increase the urinary elimination of chromium. Cr Supplementation during 6 months may be prescribed in a forms variety: Cr-chloride, Cr-nicotinate, Cr-propionate, Cr-histidinate or Cr-picolinate leads to a significant decrease HbA1c and AGE [86, 87]. Cr supplementation effects appear to be mediated by AMP kinase activation and p38 MAP kinase signaling pathway [88]. Cr controls body fat and body weight by satiety mechanisms (food intake control) and thermogenesis [89]. The Cr effects are observed via the resistin and *uncoupling protein* (UCP) decoupling proteins signaling pathway [84, 90]. Otherwise, experimental animal studies have shown that Cr modulates the inflammatory state during diabetes by decreasing proinflammatory cytokines production such as *tumor necrosis factor* (TNF-$\alpha$), and interleukin IL-6 [91].

## 7. Conclusions

Glycemic homeostasis is not only dependent on hormonal control, especially insulin; but also the micronutrients such as Chromium, Zinc, Selenium, Manganese and Copper. These Antioxidant Trace Elements act as cofactors of antioxidant enzymes (SOD, GPx) which protect the glucose-dependent tissues from the deleterious effects of reactive oxygen species following oxidation of glucose.

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## Conflict of interests

The authors declare that there is no conflict of interests regarding this paper.

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