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REVIEW PAPER

SELENIUM AND COPPER IN TYPE 2 DIABETES MELLITUS – MORE DOUBT THAN CERTAINTY

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Abstract

Type 2 diabetes mellitus (T2DM) is one of the most common chronic illnesses nearly all over the world and the prevalence of this disorder is still growing. Particularly in industrialized countries, it has become the most serious global medical and public problem, next to cancer and cardiovascular diseases. Despite intensive developments in the research on T2DM pathogenesis, the impact of nutritional factors, and particularly the effect of trace elements, on the development of this disease has not been identified completely, although relationships between some elements, e.g. Zn, Fe, Cr, and T2DM have been described in detail. Critical review of the literature indicates that the majority of inconsistencies appear in studies on Cu and Se: on the one hand, these minerals have strong antioxidant properties and even insulin-mimetic action; on the other hand, an increased risk of T2DM positively correlates with a high dietary intake of Se and Cu or supplementation with these elements. High content of these minerals in diets observed in selected countries and/or increasing popularity of dietary supplementation with Se or Cu, especially among chronically ill patients including ones with T2DM, can cause distortions in the molecular pathways of glucose metabolism. The influence of these minerals on inducing diabetic complications is even more vague and depends on several factors, e.g. the body status of these and other trace elements, the type of complications and the duration of T2DM. The relationship between T2DM and the status of Se and Cu is complex and bidirectional, thus a well-balanced diet providing these trace elements in proper amounts, according to the demand of an organism, may be one of the strategies in reducing the risk of T2DM and its complications.

Keywords: type 2 diabetes mellitus, selenium, copper, trace elements, diabetic complications.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common chronic illnesses nearly all over the world. Particularly in industrialized countries, it has become the most important global medical and public problem, next to cancer and cardiovascular diseases. The prevalence of T2DM is still growing and, as it has been ascertained, over the past three decades the number of people with T2DM has more than doubled worldwide (Shaw et al. 2010, Chen et al. 2011). Among others, lifestyle is a key factor in the development of this disease. Increasing industrialization and wealth of populations, especially in the developing countries, call for changes in lifestyle and lead to increased frequency of the use of stimulants, reduced physical activity and nutritional change (Hu 2011). Currently, there is no universal approach to the best dietary intervention for T2DM, but some dietary recommendations are constant, mainly those considering the intake of macronutrients (Wheeler et al. 2010). Although micronutrients (minerals, vitamins) are not provided in large amounts in diets, they play a fundamental role in maintaining body homeostasis. Much research has been devoted to the role of trace minerals in the etiology of T2DM, and relationships between some of them and T2DM have been described in detail in the literature. For example, Zn has strong anti-diabetogenic activity through the stabilization of the insulin molecule, and it affects glucose metabolism via stimulation or inhibition of different enzymes important in glucose metabolism and in antioxidant activity (Islam et al. 2013, jansen et al. 2009). In turn, excessive dietary intake of Fe or supplementation with it may alter glucose metabolism in several different molecular-dependent mechanisms, resulting in the increasing generation of reactive oxygen species (ROS), hyperinsulinemia and insulin resistance (Liu et al. 2009, Bao et al. 2012). The majority of data pertain to the relationship between chromium and T2DM. It has been proven, mainly on rodent models, that Cr may improve glucose homeostasis via enhanced insulin sensitivity and glucose utilization through cellular signal transduction and glucose transporters (Hoffman et al. 2014, Ulas et al. 2015). However, the absence of an equally strong effect in human studies may suggest that responses to Cr in humans are different than in rodents (Vincent 2014). Critical review of the literature indicates that the majority of inconsistencies appears in studies on Cu and Se: on the one hand, these minerals have strong antioxidant properties and even insulin-mimetic action; on the other hand an increased risk of T2DM positively correlates with high dietary intake of Se and Cu or supplementation with these elements (Ekmekcioglu et al. 2001, Stranges et al. 2010, Wiernsperger et al. 2010). Despite the wealth of research concerning trace elements in the homeostasis of glucose metabolism, there is still some ambiguity regarding their impact on this illness, especially with respect to the results concerning Se and Cu

Therefore, the aim of this review is to systematically evaluate the role of Se and Cu in T2DM and development of its complications.

SELENIUM

Selenium (Se) plays a pivotal role in immunity, reproduction, thyroid hormone metabolism and redox homeostasis, as a structural component of several key enzymes, e.g. glutathione peroxidase (GPx), thioredoxin reductase (TrxR), iodothyronine deiodinase and selenoprotein P, and therefore maintaining body Se homeostasis is necessary for the proper functioning of human body (Stranges et al. 2010). The estimated average requirements (EAR) for Se is 45 μg/d for adults, although higher levels of dietary Se may be required for proper organism functioning (christensen et al. 2015). The balanced intake of Se depends on its content in food, which in turn results from the soil Se content (Laclaustra et al. 2010, Gao et al. 2011). Plant and animal food products are both good sources of Se. Among them, fish and eggs are considered to be the richest sources of Se, followed by meat, cereals and nuts (Navaro-allarcon, Cabrera-Vique 2008, Pieczynska, grajeta 2015). The median Se intake tended to be lower in Eastern European countries, the UK, some regions of China, New Zealand, Russia and Africa than in Western European countries and the USA, where Se soil levels are generally high (Combs 2001, Stoffaneller, morse 2015). Based on the available studies, the lowest intake of Se was found in Poland (ca 20 μg/d), which was at least two times lower than EAR. On the other hand, the studies performed in Belgium, France and Canada demonstrated intakes exceeding EAR (Stoffaneller, morse 2015, combs 2001). In general, the Se status in Europe is rather suboptimal, with the lowest mean value detected in Albanian adults living in Greece (Schulpis et al. 2004, Stoffaneller, morse 2015).

Compounds of Se are capable of influencing carbohydrate and lipid metabolism and thus may impact the T2DM risk. Several studies demonstrated that Se stimulated glucose transport, phosphatidylinositol 3-kinase (PI3K) activity, improved glucose transporter (GLUT1) content in cell membranes, increased tyrosine phosphorylation as well as phosphorylation of various serine/threonine kinases present in insulin signaling pathways, e.g. Akt and p70 S6 kinase (Heart, Sung 2003, Steinbrenner et al. 2011). Moreover, a recent study performed on rats has demonstrated that Se supplementation during diabetes may improve the activities of hepatic enzymes, such as lactate dehydrogenase, glucose-6-phosphatase, glycogen phosphorylase, and glucose uptake (Chen et al. 2015). Insulin-selenium (Ins-Se) simultaneous treatment of diabetic rats led to significantly better outcome of carbohydrate metabolism reflected in better results of HbA1c and fasting blood glucose (FBG) than insulin or Se treatment alone (Xu et al. 2011). The authors of this study claimed that the improvement in carbohydrate metabolism resulted from restoration of the disturbances in PI3K and GLUT4 levels in diabetic rat muscles. All these activities showed that Se had strong insulin-like features. Moreover, Se may also demonstrate potent pro-insulin action, an effect paradoxically arising from its oxidative features, because oxidants may exhibit positive signaling effects in relation to insulin action (Goldstein et al.

2005). On the other hand, as it was demonstrated in epidemiological studies, a higher Se status was related to a negative effect, principally in the case of lipid metabolism. Increased serum Se concentrations were associated with higher total cholesterol and non-HDL cholesterol concentrations (Laclaustra et al. 2010, Stranges et al. 2010). The potential mechanism behind high Se exposure affecting lipid metabolism is currently rather speculative. In a rat animal model, supplementation with Se resulted in the increased activity of the liver protein tyrosine phosphatase 1B (PTP1B), a key enzyme in the stimulation of fatty acid synthesis, as well as in the elevated insulin signaling. The increased activity of hepatic PTP1B in Se-supplemented rats led to, for example, higher liver triglyceride concentrations (Mueller et al. 2008).

The results of human studies concerning the association between Se and T2DM are equivocal. In the elderly French population, a sex-specific protective effect of higher Se status against diabetes occurrence was found (Akbaraly et al. 2010). The authors of this study showed that the risk of disturbances in carbohydrate metabolism was statistically significantly lower in men with the highest tertile of plasma Se concentration compared to those in the lowest tertile. In contrast to the study mentioned above (Akbaraly et al. 2010), Stranges et al. (2010) found that increased dietary Se intake was positively associated with the risk of T2DM and partly confirmed the results from the study on the association between Se intake and metabolic syndrome prevalence, obtained by Zulet et al. (2009). The positively correlated frequency of diabetes with high Se intake may result from redox disturbances and the accumulation of Se in pancreatic cells, thus leading to some abnormality in insulin secretion and insulin signaling (Bleys et al. 2007). Moreover, the therapeutic window of Se is very narrow and the adverse effect may occur even in the supranutritional level of Se intake, e.g. during Se-supplementation. In the light of these results, supplementation with Se is not really recommended, especially among people with pre-diabetic conditions and/or insulin resistance. These fears were confirmed in a randomized, double-blind, placebo-controlled trial designed by Stranges et al. (2007), where long-term Se supplementation (200 μg d^{-1}) and high plasma Se level increased the risk of T2DM, even among populations from areas with low Se consumption. In a cross-sectional analysis of the U.S. adults (Bleys et al. 2007), serum Se concentration was also positively associated with the prevalence of diabetes. On the other hand, in Rayman's et al. (2012) study, six-month supplementation with Se did not result in higher risk of T2DM in a population of a relatively low baseline Se status. The risk of T2DM was assessed by plasma adiponectin concentration and therefore, in order to clarify the results, it should be noticed that adiponectin is not a good biochemical indicator of T2DM and, as it was emphasized by the authors, the major limitation of their study was the high variability of adiponectin levels. Ekmekcioglu et al. (2001) also found that there was no significant relationship between plasma and whole blood Se concentrations and T2DM prevalence, although the Se level in lym-

phocytes of diabetic patients was statistically lower than in the healthy group. The lack of association between body Se status and T2DM risk, observed in the studies mentioned above (Ekmekcioglu et al. 2001, Rayman et al. 2012), was also confirmed by Flores et al. (2011).

Several factors may explain differences between the studies mentioned above. The positive relationship between Se and T2DM risk found in Stranges et al. (2007, 2010) and Bleys et al. (2007) may result generally from the high intake of Se due to the high soil Se content in the U.S. In Europe, the dietary Se intake is lower than in the U.S. (Johnson et al. 2010) and therefore no adverse or even advantageous effect of Se supplementation on T2DM prevalence was observed in the studies performed on this continent.

Selenium in diabetic complications

Several pathological mechanisms are involved in diabetic complications, for instance polyol pathway, intracellular production of advanced glycation end product (AGE) precursors, protein kinase C (PKC) activation, increased hexosamine pathway activity. Among these completely different links, the most common feature for all cell types damaged by hyperglycemia is an increased production of reactive oxygen species (ROS) (Brownlee 2005). As stated previously, Se is involved in redox status homeostasis, thus it may play a role in the occurrence of complications of diabetes. Kumar (2012) found that patients with diabetic complications had two-fold lower Se levels compared to the control subjects. But in Sotiropoulos's et al. (2011) study, serum Se concentration did not differ between the diabetic subjects with and without coronary artery disease. Although the impact of Se status on diabetic complication prevalence is difficult to estimate, several experimental studies were performed to show that treatment with Se-inorganic and organic compounds can prevent complications of diabetes. Reddi and Bollineni (2001) tested the hypothesis whether Se-supplementation with sodium selenite may prevent renal damage in diabetic rats. In this study, the Se-supplemented rats were found to have significantly higher mRNA expression of antioxidant enzymes: CuZnSOD, catalase and GSH-Px and reduction of TGF- ß1 than the non-supplemented ones. Moreover, in the Se-treated rats, glomelural sclerosis was normalized and the interlobular artery in the cortex was greatly enlarged, which confirmed that Se may prevent or even reverse the prevalence of renal diabetic complications. In other animal studies it was shown that ebselen, a lipid-soluble, low molecular weight seleno-organic compound, had a protective role against diabetes-associated nephropathy (Chander et al. 2004, Chew et al. 2010) and atherosclerosis (Chew et al. 2009, 2010). Similar results were obtained for an ebselen analogue, such as m-hydroxy-ebselen (Tan et al. 2013).

It cannot be clarified yet whether increasing consumption of Se may influence diabetes prevalence and diabetic complications. Perhaps the problem is multifactorial and depends on an area, race, sex and co-existing of other

T2DM risk factors. Furthermore, current evidence concerning the Se-diabetes relationship does not unequivocally confirm whether disturbances in Se status are contributions to or rather results of T2DM developing.

COPPER

Copper as an essential trace element, being responsible for electron -transfer reactions and playing an important role in human metabolic processes. Dietary intake is the major source of this trace element, hence diet is crucial in risk assessment (Sadhra et al. 2007). The adequate intakes (AI) for women and men are 1.3 mg d^{-1} and 1.6 mg d^{-1}, respectively (EFSA Panel ... 2015) while net gains are observed above 2.4 mg d^{-1} (Bost et al. 2016). For comparison, estimated daily Cu intakes for people from the European Union are in the range of 0.8 - 1.8 mg (Sadhra et al. 2007). The lowest Cu intake was observed in Germany, while the highest one was notedin Belgium, findings closely connected with the Cu content in cropss and farm animals in these regions (Sadhra et al. 2007). In general, the Cu content of food is highly variable. The richest sources of Cu are meat, oysters and chocolate (Olivares and uauy 1996), although high levels of Cu are also present in nuts and wholegrain cereals (Buttriss and Hughes 2000). Overall, milk and dairy products are poor sources of this micronutrient (Gaucheron 2011). Cu is a cofactor of many enzymes, like mitochondrial cytochrome-c-oxidase, Cu-Zn dependent superoxide dismutase, and others. Owing to its unique electron structure, Cu is essential in cellular respiration, antioxidant defences, neurotransmitter functions and others. On the other hand, Cu acts as a pro-oxidant and may potentiate radical generation (Harris, Gitlin 1996). This action results from the participation in Haber-Weiss and/or Fenton reactions (as well as Fe). Moreover, Cu can indiscriminately bind to proteins by thiol and amino groups, which contributes to the wide toxicity of this element (Letelier et al. 2010). The ambiguous Cu effect on redox status has been broadly reported (Letelier et al. 2010, Qazzazz et al. 2013) and altered Cu metabolism may participate in the development of several serious illness, e.g. cancers and diabetes mellitus (Goodman et al. 2004, Talaei et al. 2011)

Cu metabolism as well as the metabolism of other trace metals can be altered in diabetic condition (Serdar et al. 2009, Flores et al. 2011). Flores et al. (2011) found that serum Cu concentration was significantly higher in diabetic patients than in healthy subjects, although there were insignificant differences in urine Cu concentration. This observation was supported by another study (Walter et al. 1991). Moreover, Serdar et al. (2009) found that Cu significantly positively correlated with HbA1c% and glucose level. On the other hand, Idonije et al. (2013) did not show differences in Cu concentrations between healthy and diabetic subjects, while Basaki et al. (2012) found even lower serum Cu concentration in diabetic patients than in healthy ones.

Impaired glucose metabolism promoting an elevated glucose level may cause an excessive intracellular Cu concentration through increased levels of

glycation end products and glycoxidation products. Some glycated proteins can bind Cu two to three times more effectively than non-glycated ones. Importantly, Cu bound to glycated proteins appeared to be active in the redox reactions (Qian et al. 1998).

Masad et al. (2007) found a novel Cu-dependent mechanism for degeneration of islet cells in T2DM. In their experiment these researchers clearly demonstrated that H_2O_2 is directly generated during aggregation of amylin, and this stimulation of H_2O_2 production is strongly Cu-dependent. In T2DM, the level of amylin is closely connected with the demand for insulin, hence it is thought that amylin aggregation is related to insulin concentration. Moreover, amyloid formation in islets leads to the reduction of beta-cell mass and can contribute to progressive failure of islets' functions (Masad et al. 2007).

Cu may also show an antioxidant capacity and prevent tissue damage caused by high glucose concentration. Qazzaz et al. (2013) reported strong antioxidant activity of copper (II) 3,5-diisopropyl salicylate. This Cu-complex was able to protect against streptozotocin-induced diabetes in rats. Pretreatment with the Cu-complex prior to a streptozotocin injection significantly reduced hyperglycemia and the level of 8-hydroxy-2'-deoxyguanosine (8-OH--2'-dG), which is a marker of DNA damage and mortality rate.

Copper in diabetic complications

As mentioned above, extracellular Cu overload may be implicated an a pathomechanism of some diabetic complications, e.g. diabetic cardiovascular diseases. Cu chelators can improve left ventricular hypertrophy, left ventricular function as well as the aortic structure and can reverse cardiac fibrosis in the rat model of diabetes (Cooper et al. 2009, Lu et al. 2013). In an animal, such as streptozotocin-iduced diabetic rat model, Zhang et al. (2014) found positive results of 8-week treatment with the Cu chelator triethylenetetramine (TETA). In rats, a decrease in left-ventricular Cu concentrations was significantly associated with the occurrence of diabetes, but the former unexpectedly normalized after the treatment. The signficantly lower myocardial Cu concentration resulted mainly from a significant decrease of intracellular Cu (I) (which comprises ca. 95% of total body Cu), while extracellular cardiac Cu (II) increased. Research results suggesst that a heart failure during diabetes may be partially explained by altered distribution of the two Cu valence states. TETA additionally normalized myocardial Cu (I) and increased levels and cell-membrane localization of copper transporter-2 as well as the SOD1 activity. Moreover, chelating extracellular Cu evoked an increase of Cu-transporting-ATPase-1level, which is depressed by diabetes.

In a human study, Talaei et al. (2011) found that urine Cu concentration is significantly higher in diabetic patients with nephropathy compared with patients without diabetic renal damage. The authors did not find any significant effects of HbA1c and diabetes durations on urinary Cu concentrations,

thus it was stated that the higher urinary Cu levels in patients with renal complications compared to the group without renal damage was the result and not the cause of diabetic nephropathy. On the other hand, there are studies indicating no altered Cu concentrations in diabetic patients' nephropathy (Prabodh et al. 2011).

CONCLUSIONS

In the development of T2DM and its complications, the body's trace mineral status plays an important role. Proper dietary intake of Se and Cu may prevent T2DM development owing to their antioxidant properties (Se, Cu) and insulin-mimic action (Se). It may also influence the activity of important enzymes in carbohydrate metabolism (Se). On the other hand, high concentrations of these minerals in diets or supplementation with Se or Cu can result in disturbances in the molecular pathways of glucose metabolism and therefore in the increased risk of T2DM and its complications. This indicates that the relationship between T2DM and the status of Se as well as Cu is complex and bidirectional, therefore a well-balanced diet providing these trace elements in proper amounts, according to the demand of an organism, may be one of the strategies in reducing the risk of T2DM and its complications.

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