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Potential of selected Trace Elements in Patients with Diabetes Mellitus
Review

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Abstract

Based on the high prevalence, diabetes mellitus (DM) is considered as a worldwide problem. More than 8.3 % of the world population is suffering from this disease. One of the causing factors of this disease can be the absence or imbalance of trace, essential elements. It can cause collapses of antioxidant defence and glucose intolerance. It plays a role in the pathogenesis and progression to diabetes mellitus. This review focuses on chromium, copper, selenium, vanadium, and zinc. Many studies deal with these elements but there is variability in opinions. Insulin-mimetic activity and ability to control the concentrations of blood glucose were confirmed. However, these effects were of more importance in patients with prediabetes. In patients with prediabetes, due to the supplementation of selected trace elements, it is possible to normalize the blood glucose level and prevent the development of diabetes mellitus. The importance of supplementation was confirmed for chromium and zinc. The supplementation of vanadium has a positive effect on the normalization of glycaemia but it is necessary to control the level as it can have toxic effects during long-term treatment. Conversely, higher copper concentrations in the body adversely affect patients and chelation therapy is needed. Selenium must be kept in the standard concentration and regular control of the concentration in the body is necessary. For this reason it is necessary to continue with analysis and the creation of new methodologies that could unify the view on the issue.

Key words: diabetes mellitus, prediabetes, chromium, copper, zinc, selenium, vanadium

INTRODUCTION

Based on the high prevalence, diabetes mellitus (DM) is considered as a worldwide problem. More than 8.3 % of the world population is suffering from this disease. DM is a non-homogeneous group of chronic metabolic diseases of various etiologies the common dominator of which is hyperglycaemia and glycosuria (1, 2, 3). DM is divided into: Type 1 diabetes (insulin-dependant diabetes), Type 2 diabetes (non-insulindependant diabetes), Gestational diabetes, and Specific types of diabetes. Type 1 diabetes is Immune-mediated diabetes. Causing factors of type 2 diabetes are unhealthy lifestyle (unhealthy eating, lack of physical activity, smoking, etc.) and intervention of the body by medication or surgical procedures. Another cause is the absence or imbalance of trace, essential elements, which can cause collapses of antioxidant defence and glucose intolerance. It plays a role in the pathogenesis and progression to type 2 diabetes. In this case the glucose imbalance status can still be altered, i.e. improved. One of the ways to improve the health of patients is to focus on the essential elements in the body. Chromium, copper, selenium, vanadium, and zinc are the elements that can control the concentrations of blood glucose and they have an insulin-mimetic potential (3, 4, 5).

Information about trace elements in the body can be obtained from full blood, plasma, and serum, but the most accurate data is from blood cells. This is explained by the fact that basic trace elements such as chromium, copper, selenium, vanadium, and zinc are naturally participated in various enzymatic processes at the molecular cellular level. According

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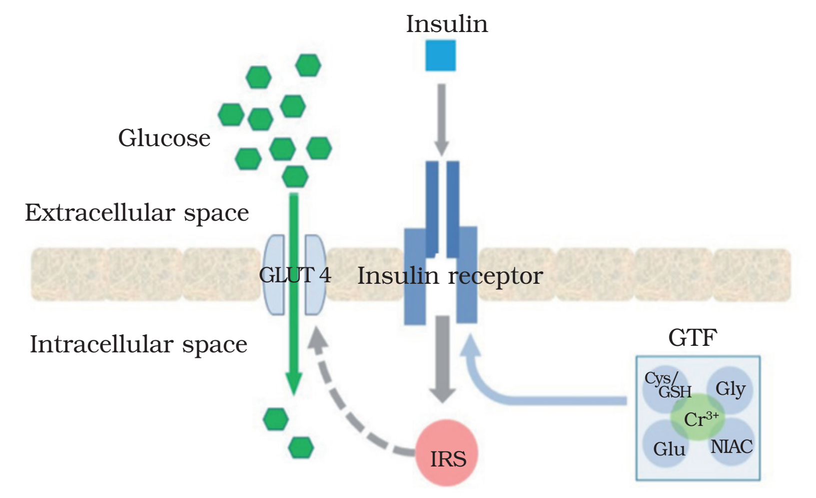
to the role of the trace element in the organism we need to select the right biological material for detection (4). Italian scientists took a very unusual biological material – tears. The advantage of the method was its non-invasive character. They found that there were significantly higher levels of zinc, chromium and cobalt, manganese, barium, and lead in the tears of diabetic patients than in a healthy control group (7).

For the detection of trace essential elements the Atomic absorption spectroscopy (AAS) was previously used; however, at present time, the most widely used technique is the Inductively Coupled Plasma with Mass Spectrometry (ICP-MS). It is one of the most sensitive, ultra-trace methods in the analytical chemistry (8). The ICP-MS operates with a very low detection limit, which allows the determination of direct samples at low concentrations. The advantages of ICP-MS are precision and wide linear dynamic range to create a standard calibration curve. Certain limitations of this technique are polyatomic interferences and matrix effect from samples rich in complex matrix (e.g., biological material) (9). However, recent research in ICP-MS have increased sensitivity and improved the possibilities for reducing interference by using a reaction or collision cell. It effectively reduces the naturally occurring matrix polyatomic interferences, thereby increasing the functionality, accuracy, and reliability of ICP-MS (10).

Due to the variability in opinions of the role and effect of essential elements in diabetes mellitus this review offers an overview of research information. It focuses on elements such as chromium, copper, zinc, selenium, and vanadium in connection with diabetes mellitus.

Chromium

The positive effect of chromium (**Cr**) was recorded 50 years ago. It plays an important role in the metabolism of sugars and fats in the body. However, it should be noted that the positive effect is only from trivalent chromium (Cr^{3+}). Hexavalent chromium (Cr^{6+}) is a proven human carcinogen of Group I according to IARC (International Agency for Research on Cancer) (8, 11). Cr^{3+} is considered as a trace, essential element which helps to eliminate excess glucose from the body. The nicotinic acid, gylcine, glutamic acid, cysteine, glutathione, and Cr^{3+} (as an active component) create the glucose tolerance factor (GTF). It affects insulin receptors, improves their sensitivity, and increases intracellular signalling, promoting the peripheral effect of insulin (Fig. 1). Based on this mechanism supplementa-



GTF – Glucose Tolerance Factor, **NIAC** – Nicotinic Acid, **Gly** – Glycine, **Cys/GSH** – Cysteine or Glutathione, **Glu** – Glutamic acid, **IRS** – Insulin Receptor Substrate

Fig. 1 Interaction of the Glucose Tolerance Factor on the Insulin receptor tion of the Cr^{3+} appears to be a useful tool against the occurrence of various manifestations of the metabolic syndrome, such as diabetes mellitus or obesity (11, 12, 13, 14). The safe amount of trivalent chromium is presented in food such as meat, fish, seafood, eggs, dried beans, mushrooms, berries, yeast, stevia, etc. A recommended daily reference dose of Cr^{3+} is from 20 to 35 μg, depending on age and gender (15). Insufficient amount of trivalent chromium in the organism and its increased need for prediabetic patients are continually being investigated. There are synthesized novel trivalent chromium complexes with unique ligands. These ligands improve the effect of Cr^{3+}. The monitored ligands that form complex with trivalent chromium are picolinic acid, niacin, niacinamide, D-phenylalanine, and salicylic acid (16).

To investigate the molecular basis of interaction of trivalent chromium with insulin and its role in glucose metabolism a spectroscopic (e.g., ICP-MS) and crystallographic analyzes were used. Based on the laboratory and the clinical studies the capabilities of trivalent chromium are:

- overcome of insulin resistance,
- slowing down the onset of diabetes mellitus,
- inhibition of the formation of free radicals,
- reduction of systolic blood pressure (11, 15).

Copper

The trace, essential element copper (**Cu**) is a cofactor of enzymes involved in many metabolic processes (e.g., glucose metabolism). The peroxidation effect of copper, which causes the reduction of the promoter activity of the insulin gene, contributes to the development of prediabetes and then to DM (17, 18, 19, 20). Interaction between insulin and Cu (I)-ATPase has been shown as a key to the active transport, distribution, and elimination of Cu ions. However, when the homeostasis of the copper is disturbed it starts to accumulate in the body (18). Many studies have found that copper concentrations in diabetic patients were higher than in the control group. Increased concentrations of Cu were determined in whole blood, plasma, and blood cells, with the exception of polymorphonuclear leucocytes (4, 18). This fact was confirmed in Japan in 2018. During supplementation and increased doses of copper in patients with prediabetes the risk of diabetes mellitus type 2 increased (17).

As a therapeutic scheme for the normalization of the damaged copper balance in the organism and to slow down the onset to type 2 diabetes, it is an alternative treatment of chelation of copper from the organism (18).

Selenium

Selenium (**Se**) is another trace element in the human body with insulin-mimetic potential that acts in suppressing DM. Se is part of the enzymes which provide redox balance, protect against oxidative stress, and then can reduce insulin resistance. However, the relationship between selenium and DM is still ambiguous. Because of the antioxidant properties selenium may be able to prevent the development of DM. However, recent studies have pointed to the fact that the deficiency or excess of Se may be related to the development of DM (4, 5, 6). Different studies offer different opinions regarding patients with DM and the amount of selenium in the body. For example, patients with insulin-dependent disorder had a low selenium concentration in erythrocytes. In another study the patients with DM had a higher concentration of selenium in serum compared with the control group (7).

Jamilian et al., in 2018, focused on the patients with Gestational Diabetes Mellitus (GDM). This disease manifests with insulin resistance and impaired glucose tolerance during pregnancy. They have found a correlation between GDM and supplementation of selenium. The Se supplementation in women with GDM significantly decreased gene expression of TNF-α and TGF-β, and significantly increased gene expression of vascular endothelial growth factor (VEGF). Se supplementation may give advantages of a therapeutic effect for women with GDM (21).

Vanadium

In nature, vanadium (**V**) is a relatively common element; approximately 0.02 % of vanadium is in the earth's crust as a part of the minerals. The average concentration of ingested vanadium from foods such as mushrooms, parsley, or black pepper is 60 µg per day. In living organism it is as essential component of enzymes at low concentrations (0.014 – 7.2 µmol/l). It exists in the complexed with proteins such as transferrin, albumin, and hemoglobin which transports it to the tissues (liver, heart, kidney, brain, muscle, and fat tissue) (5).

Vanadium exists in several oxidation states, especially as trivalent, tetravalent, and pentavalent. Metavanadate (VO^{3-}) is the most common in extracellular body fluids, whereas vanadyl (VO^{2+}) occurs mainly intracellularly. VO^{2+} can bind to the same place as Fe^{3+} in transferrin and hemoglobin, as discovered by the electron paramagnetic resonance spectroscopy (5, 22).

Diabetes mellitus is a worldwide problem with many studies existing to find a suitable medicine. One of the newest options is vanadium supplementation. However, the relationship between vanadium and diabetes mellitus is still indefinite. The studies with the supplementation of vanadium compounds provide different results. For example, after oral supplementation of vanadyl sulfate at 1.0 mg/kg/day for 2 – 4 weeks for patients with non-insulin-dependent DM morning glucose decreased by 15 – 20 %. The antidiabetic potential of vanadyl sulfate has been confirmed by rat tests. The effect of sodium metavanadate was different. The dose of sodium metavanadate (125 mg / day) for 2 weeks did not affect blood glucose level. The difference in effect can be explained by the fact that vanadyl is an active intracellular form of vanadium, while metavanadate is an extracellular form. However, in another study, the supplementation to obese patients of vanadyl sulfate, 50 mg two times per day, did not change insulin sensitivity (5, 23). The optimal dose of vanadium is important because error in the dose volume of vanadium was toxic in experimental animals (22).

A new strategy that can significantly increase the positive potential of vanadium in the impairing of glucose tolerance and metabolic syndrome is the use the vanadium complex with existing drugs as a metformin. For example, vanadyl rosiglitazone is the complex with metformin which already has a proven potential in improving diabetic symptoms (5).

Zinc

The last one of the essential trace elements in this review is zinc (**Zn**). In the body it only exists in a cationic divalent form (Zn^{2+}), so it does not have an oxidative-reductive character. Based on this fact it has become an universal and necessary element for many biochemical and physiological processes in the body. This is evidenced by the fact that about 10 % of the human genome encodes about 3000 zinc-binding proteins (24, 25). The positive insulin-mimetic activity of the zinc has been established in patients of type 2 diabetes. Zn^{2+} are involved in the transduction of the insulin receptor signal and consequently the accumulation, secretion, and distribution of insulin are positively affected. By regulating essential pathways involved in glucose homeostasis, Zn^{2+} facilitates insulin-induced glucose transport in peripheral tissues such as muscles (17, 26).

Zinc is often described in metabolic disorders and especially as regards to diabetes mellitus, as decreased. The lower plasma zinc concentrations correlated with an increase of hyperglycaemia. Interpretation of decreasing zinc concentrations in plasma may be a sign of its lack in glucose metabolism. In the analysis they also noted an increase in Zn concentration in erythrocytes. It can be due to the transport of Zn from plasma to erythrocytes (4).

The studies focused on the zinc concentrations independent of diabetes mellitus did not have identical results. The studies of German scientists Kruse-Jarres and Rükgauer have found that concentrations of Zn in diabetic patients were increased in all blood fractions. They indicate if the DM is present, Zn loses mimetic activity and accumulates in the body (4). The Japanese scientists have researched the risk group of patients with prediabetes and genetic predisposition to DM. They found that supplementation of zinc over a five-year period lead to the delay of type 2 diabetes (17). Ranasinghe et al. also researched the supplementation of zinc. They have evaluated the effect of zinc to the glycaemic balance in patients with prediabetes. The dose of 20 mg of zinc per day reduced blood glucose, insulin resistance, and improved function of β-cell. In addition, it had beneficial effects on blood pressure and cholesterol. The progress to the diabetes mellitus was slower (27).

CONCLUSION

This review offers an overview of recent researches about the metabolism of some trace elements such are chromium, copper, selenium, vanadium, and zinc in patients with diabetes mellitus.

The results of studies in relationship to prediabetes and diabetes mellitus are ambiguous. Differences among the authors of the individual studies may be due to the use of different screening methods or by tracking different sets of probands. The type of investigated sample is another possible reason for the different outcomes in studies. The trace elements have different roles in metabolism and their transport through the cells membrane is different, too. For these reasons the studies with analysis of whole blood offer different result to studies with analysis of serum, plasma, or erythrocytes. It is inappropriate to compare studies with different investigated samples because the concentrations are different in individual blood components.

In addition, the diabetes mellitus is chronic multifactorial metabolic disease. It is caused by mutations in more than one gene. It is influenced by many environmental factors, too. For example: Type 2 diabetes in a patient could have been caused by medical treatments, eating habits, life style, or the different concentrations of the trace elements in the body. However, a group of patients with prediabetes appears to be the most suitable for investigating the effect of trace elements and for changes in life style.

Some work suggests that supplementation of chromium, zinc, vanadium, and selenium may delay the onset of prediabetes and sometimes type 2 diabetes. However, if type 2 diabetes is already present, supplementation is ineffective. This knowledge could be of importance in the prevention of DM in persons with a predisposition. The new trace element complexes have a positive effect on blood glucose stabilization and although they cannot treat DM they can support treatment and have the potential to prevent the development of acute or chronic complications.

From the presented knowledge it is obvious that the role of trace elements in the prevention and treatment of prediabetes or diabetes mellitus is still unclear. The importance of supplementation was confirmed for chromium and zinc. The supplementation of vanadium has a positive effect on the normalization of glycaemia but it is necessary to control the level as it can have toxic effects during long-term treatment. Conversely, higher copper concentrations in the body adversely affect patients and chelation therapy is needed. Selenium must be kept in the standard concentration and regular control of the concentration in the body is necessary. For this reason it is necessary to continue with analyses and in the creation of new methodologies that could unify the view on the issue.

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