Micronutrients and diabetes: the case of minerals

ABSTRACT
Minerals are essential nutrients for the body. They are inorganic in nature, giving them the characteristic of being resistant to heat. Minerals are involved in a variety of chemical reactions in metabolism, regulating electrolyte balance in maintaining bone, in the process of blood clotting and the transmission of nerve impulses. Their role as enzyme cofactors is a key in various physiological processes. Glucose homeostasis involves a fine coordination of events where hormonal control by insulin plays a key role. However, the role of minerals such as magnesium, zinc, chromium, iron and selenium in diabetes is less obvious and in some cases may be controversial. This review offers information for these five elements and their correlation with diabetes.

Key words: minerals and diabetes, magnesium, zinc, selenium, iron, chromium.

Maria de los Ángeles Granados-Silvestre1
María Guadalupe Ortiz-López1
Isela Montúfar-Robles1
Marta Menjívar-Iraheta2

1Unidad de Investigación, Laboratorio de Endocrinología Molecular, Hospital Juárez de México, Secretaria de Salud, México, D.F., México
2Laboratorio de Diabetes, Departamento de Biología, Universidad Nacional Autónoma de México, México, D.F., México

Received: 2-21-2013
Accepted: 9-12-2013

Correspondence
Dra. María de los Ángeles Granados Silvestre
Hospital Juárez de México
Av. Instituto Politécnico Nacional 5160
07760 México, D.F., México
Tel: (55) 5747784
E-mail: francisella@hotmail.com
INTRODUCTION

Micronutrients are among the minerals required by organisms in trace concentrations sufficient to maintain correct homeostasis. Deficiency of these elements may cause different health problems. Type 2 diabetes mellitus (T2DM) and its chronic complications may be associated with an alteration of some minerals in plasma, tissues and urine.

Biochemical Function of Micronutrients

Trace elements are involved in various physiological processes, particularly in immunity and metabolism as cofactors participate in the modulation of enzymatic activities or are an important part of enzymes as prosthetic groups. Zinc (Zn) is a co-factor of ~100 enzymes, whereas selenium (Se) is required in the selenocysteine form for the glutathione peroxidase enzyme. Minerals are important in genetic control such as zinc in the “zinc finger”, the reason why it is present in a transcription factor that binds DNA to regulate the genetic transcription of numerous proteins necessary for cell function.

Minerals also comprise part of the antioxidant complex. Through their metabolism the organism is able to generate reactive oxygen species that damage, in particular, the cell membrane and nucleic acids. This potential damage is limited by mechanisms that interact directly with the reactive oxygen species such as the enzymatic systems that transform the products of oxidation: superoxide dismutase enzyme (dependent of Zn/Cu or Mn), glutathione peroxidase (dependent on selenium) and catalase (dependent on iron). Also, chromium (Cr) participates in the homeostatic regulation of glucose and fat metabolism and magnesium (Mg), the second most abundant intracellular cation, is involved in energy metabolism, in the synthesis of proteins and in the modulation of glucose transport across the cell membrane.

During illness, the nutritional status is affected especially by the combination of increased demand due to nutrient losses when there is decreased consumption, which particularly affects the status of the micronutrients.

Mineral Status and Diabetes

Many studies relate alterations in mineral homeostasis with T2DM and cardiovascular diseases. In experimentally induced streptozotocin (STZ) diabetic rats, the mineral balance is altered as a result of damage to pancreatic function.

Magnesium

Decrease in magnesium intake has been associated with increased risk of metabolic syndrome and T2DM. It is estimated that persons with diabetes have a higher risk of having low concentrations of magnesium. Clinical studies suggest that magnesium supplements may improve glycemic control.

Magnesium is the second most important cation after potassium. It is absorbed through the small intestine and is excreted in the urine. Plasma concentrations of magnesium in healthy adults are constant and are between 0.75 and 0.96 mmol/L (mean of 0.85 mmol/L). Magnesium is a necessary co-factor for carrying out >300 enzymatic reactions, specifically in the processes of phosphorylation and, in general, in those where the use or transference of ATP is necessary. Intracellular magnesium regulates the action of insulin. Deficiency of this cation inhibits the acute phase of insulin in response to an oral glucose load. It is associated with resistance to insulin, promotes uptake of insulin by cells and maintains vascular tone. Decrease of intracellular magnesium may cause a deficiency in tyrosine kinase activity, which alters insulin sensitivity by controlling the activity of the receptor after its union. It may also damage intracellular signaling.
Diabetes is associated with an extra- or intracellular loss of magnesium. In patients with T2DM the plasma concentrations of magnesium are inversely correlated with metabolic control. At the cellular level, cytosolic free magnesium is reduced in subjects with T2DM. The association between magnesium deficiency, insulin resistance and T2DM is strongly supported by the observation of various treatments for diabetes that appear to increase the concentrations of magnesium. Thus, metformin elevates the concentrations of magnesium in the liver, piroglitazone could increase insulin sensitivity with a positive effect on the magnesium metabolism in vitro and in vivo stimulating the concentration of magnesium in adipocytes and increasing serum magnesium in subjects receiving the medication.

It has also been proposed that magnesium deficiency plays an important role in the appearance of diabetic complications. Ionic intracellular changes are related with cardiovascular structural changes that many times co-exist in diabetic individuals. It has been suggested that this damage is related to inositol transport because this mechanism is affected when there is loss of magnesium. Among the most important mechanisms related with the loss of magnesium in diabetes are low consumption and increase in urinary loss because absorption and retention of magnesium are not damaged in patients with T2DM.

**Zinc**

Zinc is one of the most important trace elements in the body. Its deficiency is associated with a variety of defects including anorexia, skin lesions and developmental delay. Molecular studies have demonstrated that zinc deficiency affects the genes involved in multiple cell functions. In particular, it decreases the metallothionein expression, a growth factor similar to type 1 insulin, the transporter protein of the growth factor similar to insulin and cycline d1 involved in cell proliferation.

Zinc deficiencies have also been correlated in persons with diabetes. Zinc plays important roles in insulin homeostasis. Its deficiency has been associated with insulin resistance in patients with T2DM. The relationship between insulin and zinc was described at the beginning of the 1930s when it became commercially available. The in vitro addition of zinc (protamine) prolongs the action and half life of insulin and delays its absorption from the site of injection to the site where it will exert its effect. When there is zinc within a cell, the monomere of insulin assembles to form a dimer, which is its storage and secretion form. To a neutral pH, insulin dimers are assembled to form a hexamere. This is a stable conformation and commonly used pharmacologically. Hyperglycemia due to type 1 or 2 diabetes causes an important loss of zinc that could aggravate the diabetic condition in secondary complications, mediated in part by the oxidative stress because this mineral is a decisive factor in the antioxidant cellular defense. When it is insufficient, cellular damage may be irreversible. Prost et al. suggest that zinc has a predominant role in insulin secretion by regulating potassium channels. Bancila et al. propose that when zinc is bound to two residues of histidine (histidina) (H326 and H332) in the subunit SUR1 it activates the KATP channels. The protective effects of zinc have been demonstrated in animal models of T2DM. A diet high in zinc (1000 mg Zn/kg) for 4 weeks in ob/ob mice decreased hyperglycemia and hyperinsulinemia and elevated insulin in the pancreatic islets. Wolman et al. found that many patients lose large quantities of zinc via the intestinal tract, a loss that can be replaced with mineral-containing supplements. The positive balance of zinc is associated with an increase in plasma insulin. For this reason, adequate administration of the
mineral is necessary to stimulate synthesis of this hormone that increases the activity of many zinc-dependent enzymes in the pathways in protein synthesis and promotes adequate insulin response to glucose utilization.

**Chromium**

Chromium is a trace element that is found in low concentrations in diabetic individuals. Therefore, its administration may help improve glycemic control. Supplements such as trivalent chromium as part of the treatment of patients with T2DM and other diseases related to insulin resistance began to be prescribed in 1975, immediately after the discovery of a substance found in Brewer’s yeast that helps to decrease the age-related glucose intolerance (the test was conducted in older rats).

This substance was identified as \( \text{CR}^{3+} \). In 1977, \( \text{CR}^{3+} \) was declared as an essential nutrient. It was noted that hospitalized patients who received parenteral nutrition deficient in \( \text{CR}^{3+} \) had significant elevations of plasma glucose and that their glucose concentrations normalized after \( \text{CR}^{3+} \) was added to their diet.\(^{27}\)

Addition of chromium to the diet maintains glucose tolerance, reduces body fat, increases the lean muscle mass and sensitivity to insulin.\(^{28}\) There are controversies with regard to the effectiveness of chromium in this regard; however, the discrepancies may be due to the doses indicated in each study. It is reported that a dose of 100 mg/day of chromium is not effective,\(^{29}\) but a dose of 200-1000 mg daily is effective.\(^{30}\) More studies are needed in specific populations in order to clarify if the discrepancies in the beneficial effects are due to the dosage or genetic factors of the population that could modify the response.

The molecular basis of the action of \( \text{Cr}^{3+} \) has been long studied. Recently, an intracellular low molecular weight octapeptide was described known as chromomoduline, which increases the response of the insulin receptors.\(^{31}\) Chen et al.\(^{32}\) reported that treatment with \( \text{CrCl}_3 \), mobilizes the glucose GLUT4 transporter towards the plasma membranes in the adipocytes. Together with this finding, glucose transporter also increased when stimulated by insulin, which suggests that chromium acts along with other mechanisms as the increase in membrane fluidity by decreasing the cholesterol that is present.

**Selenium**

Selenium (Se) is an essential trace element that participates in the complex enzymatic system of defense of the organism against oxidative stress. In this context the better characterized selenoenzymes are the families of the glutathione peroxidase, deiodinase iodothyronine and reductase thioredoxin. These selenoenzymes, in addition to acting as antioxidants that modify the redox state, participate in cellular development, in the processes of apoptosis, and in the cell signaling pathways as well as being part of the transcription factors. They also modify thyroid hormone metabolism and are responsible for the transport of selenium to the tissues. The selenoproteins incorporate selenium in the form of selenocysteine and is totally ionized to physiological pH, acting efficiently in the redox catalysis.\(^{33}\)

The role of selenium in diabetes is controversial. There is evidence in animal models of diabetes induced by STZ where selenium normalizes glucose concentrations and modifies the enzymatic systems that participate in hepatic glycolysis and gluconeogenesis without involvement of insulin regulation.\(^{34}\) It is suggested that selenium exercises similar effects to insulin in glucose metabolism due to stimulation of tyrosine kinases involved in the insulin signaling cascade.\(^{33}\) Human studies have demonstrated that a high
serum concentration of selenium is positively associated with the prevalence of diabetes. The possible diabetogenic effects of an excess of selenium may be paradoxical events because some components of this mineral are capable of generating reactive oxygen species and accumulate in the pancreatic tissue of various animals. Under conditions of oxidative stress, reactive oxygen species could increase insulin resistance and affect β-pancreatic function.

Iron

Iron (Fe) has various vital functions in the organism: oxygen transport to the red blood cells, electron transfer within the cell, and as an integral part of the enzymatic system in various tissues. Iron is stored in the liver as ferritin and hemosiderin and is transported to the different parts of the body in transferrin protein. It is suggested that the accumulation of iron contributes to the formation of free radicals and oxidative stress. For this reason, careful control of the availability of iron is fundamental for maintaining normal cellular function.

The generation of reactive oxygen species by oxidative metals such as iron may be involved in the pathogenesis of certain diseases such as steatohepatitis and Alzheimer’s disease.

Altered hemostasis due to iron is also associated with diabetes. Increase of iron in the body has been reported as a risk factor for diabetes. Transferrin and iron induce insulin resistance and alter glucose transport in adipocytes through mechanisms independent of fatty acids.

In in vitro and in vivo studies carried out in hepatocytes, loss of iron by deferoxamine over-regulates glucose uptake, increases activity and insulin receptor signaling and stabilizes the expression of factor HIF-1α. Minamiyama et al. reported than in an animal model of diabetes the loss of iron modulated insulin concentrations, oxidative stress and pancreatic expression of PPARγ. Therefore, this treatment may offer an alternative for decreasing complications of diabetes.

In conclusion, micronutrients as minerals play an important role in metabolic and cell processes. Their deficiency due to an increase in clearance or deficiency in ingestion may contribute to secondary complications in some diseases. Their administration as supplements may be beneficial in certain stages of life such as childhood or during pregnancy. In some diseases such as diabetes, these minerals, with the exception of iron, are a good option indicated together with oral antiglycemics and antioxidants for glycemic control because they participate in decisive stages in the control and regulation of glucose and insulin. Their administration, however, should be carefully prescribed to reach the adequate doses and achieve the expected effects, avoiding reaching concentrations that may produce adverse effects.

REFERENCES

