Diabetes prevention and management: the role of trace minerals

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Introduction

Interest in the role of trace minerals in diabetes started way back in 1929, when Glaser and Halpern noticed that yeast extract potentiates the action of insulin.[1] The discovery in 1959 of glucose tolerance factor in yeast and the isolation of chromium as its active component intensified interest in the status of other trace minerals in diabetes.[2]

Trace minerals influence glucose metabolism through various means, e.g. serving as co-factors, activation of insulin receptor sites, and increasing insulin sensitivity.[3–5] Diabetes alters the homeostasis of trace minerals.[6–8] Some of these minerals, e.g. chromium, zinc, and magnesium, are excreted at higher than normal rates in the urine of diabetic patients. The polyuria of diabetes resulting from hyperosmotic glomerular filtrate is largely responsible for enhanced urinary mineral loss.[9, 10]

The relationship between diabetes and trace minerals is complex with no clear cause and effect relationship. Which comes first? The effects of hyperglycaemia on minerals metabolism, or the effects that follow alterations in trace mineral homeostasis on carbohydrate metabolism.

Controversy remains regarding supplemental minerals as adjuncts in the treatment of patients with diabetes.[11–13] Solving this problem could include increasing dietary intake of local specific food rich in these minerals or utilising supplemental sources of the mineral for those at risk of being deficient.

Methods – data sources

Our aim was to review clinical studies designed to investigate the relationship between diabetes and trace minerals, and provide evidence-based recommendations for the use of trace minerals in the treatment or prevention of diabetes. We conducted a systematic review of the literature to identify research that addresses the role, if any, of trace minerals in the aetiopathogenesis, prevention, and treatment of diabetes.

We searched MEDLINE, via PubMed, for reports in English of controlled trials using the search terms 'relationship between trace minerals/elements and diabetes mellitus,' and 'relationship between diabetes mellitus and trace mineral/elements.' We reviewed the titles and abstracts of each study. These articles were then reviewed in full.

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Trace minerals

Eating fresh grains, fruits, sea food, and vegetables grown in nutrient-rich soil and drinking mineral-rich water have been the primary supply for the full spectrum of ionically charged minerals. Naturally occurring, nutrient-rich soil is almost non-existent on commercial farms. Refining of carbohydrate foods also causes a sharp drop in the concentration of various vitamins and minerals. Drugs, e.g. corticosteroids or thiazide diuretics, can lead to significant losses of micro-minerals and induce a diabetes-like condition.[14–16]

Trace minerals play key roles in living organisms. Many are essential components of enzymes while others donate or accept electrons in oxidation–reduction reactions resulting in the generation and utilisation of energy. Others maintain the structural stability of important biological molecules and control biological processes by facilitating the binding of molecules to receptor sites on cell membranes, or by altering the structure or ionic nature of membranes and inducing gene expression resulting in the formation of proteins involved in life processes. The relative importance of the processes of absorption, storage, and excretion varies among the trace minerals. The homeostatic regulation of trace minerals existing as positively charged cations, e.g. zinc, occurs primarily during absorption from the gastrointestinal tract. Trace elements absorbed as negatively charged anions, e.g. selenium, are usually absorbed freely and completely from the gastrointestinal tract. Thus, they are homeostatically regulated primarily by excretion through the urine, bile, sweat, and breath.

Chromium

In 1955, it was noticed that brewer's yeast contained a glucose tolerance factor (GTF), later found to be a form of trivalent chromium, that prevented diabetes in experimental animals.[17,18] In humans, patients receiving total parenteral nutrition (TPN) developed severe signs of diabetes, including weight loss and hyperglycaemia that was refractory to increasing insulin dosing.[19] After 2 weeks of supplemental chromium, signs and symptoms of diabetes subsided, glycaemic control mark-

edly improved, and insulin requirements significantly reduced. Studies of the beneficial effects of chromium in patients receiving TPN have been documented and chromium is now routinely added to TPN solutions.[20,21] Trivalent chromium is found in egg yolks, whole-grain products, high-bran breakfast cereals, coffee, nuts, green beans, meat, and some brands of wine and beer.[22] Once absorbed, chromium is distributed widely in the body, with the highest levels being found in the kidney, liver, spleen, muscle, and bone.[23]

Chromium activates insulin receptor kinase and potentiates the actions of insulin. It has also been demonstrated to inhibit phosphotyrosine phosphatase, the enzyme that cleaves phosphate from the insulin receptor, leading to decreases in insulin sensitivity.[24–26] Activation of insulin receptor kinase and inhibition of insulin receptor phosphatase leads to increased phosphorylation of the insulin receptor and increased insulin sensitivity.[27] Chromium enhances insulin binding, insulin receptor number, insulin internalisation, and beta cell sensitivity.[28]

Consumption of refined foods exacerbates insufficient dietary chromium because these foods are not only low in dietary chromium but also increase its loss from the body. Chromium losses are also increased during pregnancy and as a result of strenuous exercise, infection, physical trauma, and other forms of stress.[29,30] Chromium levels are low in the elderly and in patients with diabetes.[31,32] Additionally, diabetes patients have altered chromium metabolism compared with non-diabetic persons, as both absorption and excretion are higher.[33,34] Hair and blood levels are reported to be between 33% and over 50% lower in diabetic patients compared with normal control subjects.[31,35,36] Ravina and colleagues showed that administration of chromium can reduce the requirement for anti-diabetic drugs by 50% in these patients, and also reverse corticosteroid-induced diabetes.[16]

Results obtained in studies of patients with diabetes or glucose intolerance, as well as those from normal subjects, have indicated variable effects of chromium supplementation on one or more components of the serum lipid profile.[34, 37–49]

Several human studies carried out have reported no significant effect of chromium supplementation in patients with diabetes.[37,38,43,50–52] This is however likely to be due to patient selection methods.[53] Chromium supplementation is primarily of interest in patients suffering from or likely to suffer from chromium deficiency if the aim is to reduce hyperglycaemia, or as an adjuvant to already-existing treatment with established anti-diabetic medication.[54]

Zinc

The relationship between zinc and insulin was first recognised by Scott and Fischer who found that whereas the normal human pancreas contained significant quantities of zinc, the diabetic pancreas contained very little.[55] Histochemical techniques later confirmed that zinc and insulin concentrations in the pancreas changed in the same direction in humans.[56] Severe zinc deficiency is not frequent but concerns have nevertheless been raised about zinc levels in diabetic patients because of increased excretion due to polyuria. Diabetic patients excrete more zinc in the urine than those without diabetes.[57–59] Hyperglycaemia being responsible for the hyperzincuria is supported in humans by a significant correlation between glycated haemoglobin and urinary zinc excretion.[60]

Zinc is an efficient antioxidant and has an important role in the functioning of hundreds of enzymes and in insulin metabolism.[61–63] Zinc is found mainly in cereals, meat, seafood and dairy products.[64] Approximately 90% is found in skeletal muscle and bone, and less than 0.1% circulates in plasma.[65] Zinc is considered important in metabolic diseases (e.g. insulin resistance, metabolic syndrome, diabetes), because it plays a major role in the stabilisation of insulin hexamers and the pancreatic storage of insulin. It is an efficient antioxidant, while oxidative stress is considered to be a main component in initiation and progression of insulin resistance and diabetes.[66–69] Since zinc is intrinsic to the storage and granulisation of insulin within the beta cell, and increased insulin secretion reduces beta cell zinc concentration, then there would be decreased islet cell insulin content in zinc deficiency states.[70]

Zinc reduced the risk for type 2 diabetes in a zinc-deficient subgroup,[71] while aggravated glucose intolerance was found in zinc-deficient diabetic patients.[72] Correction of oxidative stress with dietary zinc may be possible as demonstrated by an elevation of hepatic anti oxidant enzymes.[73] In microalbuminuric type 2 diabetic patients zinc lowered homocysteine levels, while in obese, non-diabetic subjects insulin sensitivity was improved.[74,75] Animal studies carried out by Minami et al showed an increase in the progression of diabetic nephropathy in diabetic rats when zinc deficiency was induced either by increased renal excretion, or by dietary induced deficiency.[76] In humans, Faure et al demonstrated some protective effect of zinc supplementation for the development of diabetic retinopathy associated with an increase in superoxide dismutase, while the observed decrease in retinopathy may be the result of decreased lipid peroxidation of the retinal polyunsaturated fatty acids.[77]

Despite the potential interest in zinc in diabetes, not many investigations have been published. The effects of hyperinsulinism/hyperglycaemia on tissue concentrations of zinc are difficult to evaluate and this may reveal interactions with or alterations in other trace elements, differential effects of hyperinsulinism or hyperglycaemia, or other factors not yet appreciated. The conclusions are far from clear and more studies are definitely required.

Selenium

Selenium is a component of enzymes that catalyse redox reactions and it acts as an antioxidant in the form of selenoproteins which contain selenocysteine.[78] The best known selenoproteins are glutathione peroxidases, thioredoxin reductases, and iodothyronine deiodinases.[79]

Food sources include fish, eggs, and meat from animals fed abundant amounts of selenium, and grains grown on high-selenium soil. Selenium, which is biologically important as an anion, is relatively well absorbed from the diet and is homeostatically regulated by excretion, primarily in the urine but some in breath.[80] Selenoproteins are responsible for the transport of selenium to tissues and severe selenium deficiency is rare, while reduced selenium levels are seen in diabetic subjects together with increased oxidative stress.[81,82] Selenium has control when very potent antioxidant and anti-inflammatory effects and thus supplementation may be considered in persons with insulin resistance and diabetes because of the role played by oxidative stress and inflammation in conditions of these conditions.[83,84]

Selenium was found to inhibit hyperglycaemia or hyperinsulinaemia-induced expression of adhesion molecules and it also reduced inflammation, C-reactive proteins and soluble L-selectin.[85,86] The effect appears to be mediated via phosphorylation of tyrosyl residues on cellular and ribosomal proteins normally involved in insulin's post-receptor effects. Battell and colleagues showed that sodium selenate improved glucose tolerance in the streptozotocin model of diabetes in rats.[87] In mice, selenate reduced gluconeogenesis and inhibited phosphotyrosine phosphatases by 50%.[88] In type 1 diabetic rats, studies have shown that selenium protected the mitochondria from oxidative stress.[89–91]

In humans, lower levels of sialic acid and triglycerides were reported in young adults having the highest dietary selenium intake and there was a reduction in complement factor 3.[92,93] There are however only a few studies available and no positive effect was found on diabetes prevention and some studies even pointed towards an increased risk.[94–96]

Magnesium

Magnesium is essential for all energy-dependent transport systems, glycolysis, oxidative energy metabolism, biosynthetic reactions, normal bone metabolism, neuromuscular activity, electrolyte balance, and cell membrane stabilisation.[97] Food sources include chocolate, dried fruits, whole grains, leafy green vegetables, legumes, nuts, and fish.[98] About one-third of an orally administered load of magnesium is absorbed in the intestines; excretion is primarily via the kidneys, but also via faeces. Several hormones help regulate magnesium levels and these include calcitonin, parathyroid hormone, and insulin. It is an important intracellular cation that is distributed into the mineral phase of bones (65%), intracellular space (34%), and extracellular fluid (1%).[99] More recent findings have suggested that as many as 25% of patients with diabetes may have suboptimal magnesium status.[100] Magnesium is one of the more common micronutrient deficiencies in diabetes.[97,101-103] Magnesium deficiencies have been implicated in insulin resistance, carbohydrate intolerance, dislipidaemia, and complications of diabetes.[104] Hypomagnesaemia in diabetes is most likely due to increased urinary losses,[102,103] and low dietary magnesium intake has been associated with an increased incidence of type 2 diabetes in some,[105] but not all studies.[106]

Although a reduced release of insulin has been reported in individuals with compromised magnesium status, most of the focus on magnesium supplementation in diabetes now involves interest in preventing long-term complications; and the widespread use of magnesium in normal metabolism of macronutrients, cellular transport systems, intracellular signalling systems, platelet aggregation, vascular smooth muscle tone and contractility, electrolyte homeostasis, and phosphorylation and dephosphorylation reactions suggests that its effects are multifactorial.[107]

Manganese

A deficiency of manganese, a cofactor for several enzymatic systems results in glucose intolerance in animals.[108,109] Also, pancreatectomy and diabetes have been correlated with decreased manganese levels in blood, while manganese supplements have reversed the impaired glucose utilisation induced by manganese deficiency in animals.[110,111]

In humans, manganese plays a role in the pathogenesis of diabetes.[112,113] High urinary manganese excretion and decreased concentrations of blood and hair manganese were observed in diabetic patients compared with a normal control group.[114–116] However, it is yet to be determined whether diabetes causes high manganese urinary excretion and low serum and hair level of manganese, or manganese deficiency contributes to the development of the glucose intolerance.[116] The pathogenetic implications and therapeutic applications are not fully understood and more investigations are needed to establish these.

Vanadium and molybdenum

Vanadium, along with its cousin molybdenum, can mimic insulin. Both can strongly inhibit protein tyrosine phosphatase activity, thus maintaining tyrosine phosphorylation in protein extracts.[117] Vanadium, though present in very small quantities, is ubiquitous in the environment, making it difficult to induce deficiency or to accurately measure it status.[98,118] In humans, vanadium can alter lipid and glucose metabolism by enhancing glucose oxidation, glycogen synthesis, and hepatic glucose output.[119,120]

Molybdenum inactivates glycogen synthase, increases glycolytic flux in rat hepatocytes, and synergistically stimulates glucose uptake in rat adipocytes.[117,121,122] Improvement in lipid levels and significant reduction of about 75% to normalisation of blood glucose levels, have been reported in diabetic rats treated with orally administered molybdenum.[123,124]

Although some signs of diabetes were improved by vanadium and molybdenum treatment, because little is known concerning the potential long-term toxic side-effects, more studies are definitely needed as the therapeutic use of these elements in diabetes appears to hold some promise.

Conclusion

Studies in both animals and humans indicate that trace minerals are essential in the action of insulin, and epidemiologic studies suggest that tissue levels of these minerals are reduced among persons with diabetes compared with healthy control subjects. However, the role of trace mineral supplementation outside of the rare deficiency states is still controversial, especially in their use for glycaemic control among diabetic patients. Most clinical studies have major limitations including small size, short term, non-randomised design, and different doses of trace mineral supplementation. Long-term trials to assess safety and effects of trace minerals treatment on diabetes, as well as metabolic parameters, needs to be carried out, even though such trials would be costly and time consuming.

Consumption of local food, fruits and vegetables containing beneficial trace micronutrients should be encouraged. Multivitamins containing trace minerals should be prescribed only when necessary. Care should be taken not to medicate what is essentially a lifestyle and dietary issue. In the future, therapy for diabetes may include nutritional supplements for people whom research has identified as having the genetic or clinical potential to benefit from them.

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