THE POSSIBLE LINK BETWEEN MINERAL DEFICIENCIES AND DIABETES MELLITUS: A REVIEW

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ABSTRACT

The increasing incidence and burden of diabetes globally calls for public enlightenment on the pathogenesis of the disease. The main cause of diabetes is unknown, however, several risk factors have been suggested, among which is mineral deficiencies in the body. This paper reviewed the mechanisms and role of mineral deficiencies in the pathogenesis of diabetes. The Google search engine and other reputable sources were used to search for relevant information. It was noted that studies have established that mineral deficiencies play a role in the onset of diabetes, but their mechanisms depend on the deficient minerals. Most minerals play important roles in the proper functioning of the body. However, minerals of great importance to diabetes are magnesium, chromium, zinc, calcium, vanadium, selenium, and omega-3 fatty acid. These minerals mimic insulin and enhance the movement of glucose into the cells where it is used as fuel or stored in adipose tissues for later use. Doses of these minerals above certain levels could increase diabetes risk. People are therefore advised to include these minerals in their diets, with advice from qualified medical personnel.

Keywords: Adipose tissues, Diabetes, Glucose, Insulin, Minerals.

INTRODUCTION

Types 1 and 2 diabetes are commonly regarded as two different diseases. However, both types are medically called diabetes mellitus or honey diabetes. This name was coined from its most obvious symptom, a honey-sweet urine. In non-diabetics, a hormone known as insulin regulates the blood glucose levels. Insulin was discovered in 1922 and known for its role in channeling glucose into muscle cells for energy production [1]. In type 1 diabetes, the insulin-producing beta cells in the pancreas are increasingly destroyed, leading to hyperglycemia. Insulin production

remains more or less normal in type 2, but sometimes insulin released into the bloodstream is blocked by a tumour of the pancreas. This leads to increasing resistance to the insulin in the blood, resulting in high blood glucose [1].

The exact mechanisms for developing both diseases are unknown. However, the development of type 1 diabetes is suspected to follow exposure to an environmental trigger such as viruses, bacteria, and chemicals, among others. For instance, viral exposure may stimulate an immune attack against the beta cells of the pancreas in some genetically predisposed people. In type 2 diabetes, one of the basic mechanisms of insulin-resistant hyperglycemia occurs when calorie taken is more than the calorie needed by the body [1]. When a human eats beyond his capacity, excess energy is stored in the body as glycogen and saturated fat. When the body has no room to store excess calories resulting from overeating, the fat and muscle cells begin to lose insulin receptors and/or lose function. This reduces the amount of insulin that enters the cells, a condition known as insulin resistance. The blood sugar rises to unhealthy levels, leaving the pancreas with no other option than to compensate and produce more insulin. The resultant elevation of insulin levels can cause a number of adverse cardiovascular, neurological and endocrine effects. If this cycle continues, eventually the insulin producing beta cells may become exhausted and lose their ability to produce insulin, resulting in "double diabetes" where one have low insulin and high blood sugar as well as insulin resistance [1].

The destruction of beta cells in case of type 1 diabetes and insulin resistance in type 2 diabetes notwithstanding, the body still has self-healing and regenerative abilities. Every minute, 60,000 cells in the body are reborn, and over the course of 100 days, approximately 17 trillion are replaced by new cells. So, if the environmental triggers of diabetes in predisposed individuals are removed, the pancreas (in some cases) can regenerate beta cell function [1].

Mineral deficiencies have been implicated as one of the environmental triggers. However, there are diverse opinions on their mechanisms of action. This paper, therefore, was intended to review and articulate the possible links between mineral deficiencies to onset of diabetes and their mechanisms.

SEARCH METHODS

The Google search engine was used to collect materials on the subject over the internet. Criteria used for article selection included educational qualifications and affiliations of the authors, the reputation of the journal hosting the article, among others.

RESULTS AND DISCUSION

Many studies overwhelmingly confirmed mineral deficiencies can lead to a host of health problems, including an increased risk for diabetes [2]. The most important minerals whose deficiencies may lead to the onset of diabetes are magnesium, chromium, zinc, calcium, vanadium, selenium, and omega-3-acid [2].

Magnesium

Insufficient cellular magnesium levels have been shown to affect metabolic function that typically snowballs into more significant health problems, including diabetes [2]. According to Damiano *et al* [3], researchers have detected 3,751 magnesium-binding sites on human proteins, reflecting how important this mineral is to many biological processes. For example, magnesium plays a role in the body's detoxification processes and therefore it is important for minimizing damage from toxic chemicals such as heavy metals, among others. Even glutathione, considered by many scientists to be the most powerful antioxidant in the body, requires magnesium in order to be produced [2].

The mechanism by which magnesium controls glucose and insulin homeostasis appears to involve two genes responsible for magnesium homeostasis [2]. Magnesium is required to activate the tyrosine kinase, an enzyme that functions as an "on" or "off" switch in many cellular functions and required for the proper functioning of the insulin receptors. It is well known that people with insulin resistance also experience increased excretion of magnesium in their urine, which further contributes to diminished magnesium levels. This magnesium loss appears to be secondary to increased urinary glucose, which increases urinary output [4]. Therefore, inadequate magnesium intake seems to prompt a vicious cycle of low magnesium levels, elevated insulin and glucose levels, and excess magnesium excretion [5].

Several studies have established the role of magnesium in insulin sensitivity, glucose regulation, and protection from type 2 diabetes. A 1996 study conducted by Overlook Hospital in New Jersey examined the link between diabetes and magnesium deficiency. The researchers found that 25 % or more of diabetic patients, either with type 1 or type 2 diabetes, were deficient in magnesium [2]. Lowered magnesium levels have also been linked to insulin resistance in elderly diabetic patients. Supplementing with magnesium could improve insulin receptors and help regulate blood sugar levels [2]. A study conducted in 2013 involving pre-diabetics found that most had an inadequate magnesium intake. Those with the highest magnesium intake reduced their risk for blood sugar and metabolic problems by 71 % [6].

Chromium

Chromium plays important roles in the prevention of type 2 diabetes because it works closely with insulin to channel glucose into cells. The higher the level of insulin in the blood, the higher is the chromium level. Thus more chromium is lost with urine after sweet meals because more insulin is produced in response to the glucose in sweet meal [7]. Chromium increases insulin receptors that bind insulin to cells, resulting in increasing utilization of glucose. Small doses of the mineral may improve lipid profiles in diabetics and deficiencies may impair blood glucose control. Ironically, while a high dose of chromium may be toxic to nondiabetics, it is nontoxic to diabetics and may even produce greater effects than low dose [2]. The importance of chromium in blood glucose regulation has prompted investigation of its mechanism of action and has been fairly understood. A molecule named Glucose Tolerance Factor (GTF) was found to be primarily composed of chromium. It is the lack of this natural ingredient, known as GTF chromium that is often referred to as type 2 diabetes. If chromium levels decrease, there is a corresponding decrease in sugar delivery of insulin. In fact, some doctors believe that diabetes is not a disease, but GTF chromium deficiency [2].

Several scientific studies have confirmed the role of chromium in maintaining a normal blood glucose level. A 2002 review of several chromium studies related to diabetes showed somewhat mixed results. One study showed that chromium supplements significantly reduced blood glucose levels in diabetics, but other studies showed no change or minor changes. These discrepancies could be due to varying doses applied [2]. Chromium works best in diabetic individuals at high doses. In some studies, 50 % of diabetics improved with additional chromium

while deficiency of chromium also raised lipid levels in the blood, thereby increasing the risk of atherosclerosis [7]. A review of 15 trials using chromium picolinate noted consistent improvements in glycemic control in 13 of the 15 trials, with an overall average decrease in glycosylated hemoglobin of 0.95% [8].

Zinc

According to Sunderman [9], zinc is required for the function of more than 300 enzymes of all classes, and it is involved in the regulation of a large number of genes [10]. Zinc participates in some hormone–receptor interactions and also in intracellular signaling [11]. Zinc is also involved in both endocrine and exocrine functions of the pancreas [11]. It is necessary to have a steady dietary or supplement intake of zinc, because the body cannot store zinc for future use. The blood glucose regulatory mechanism of zinc involves its role in maintaining a healthy function of most hormones, including insulin and does it through at least three ways.

One, zinc binds to insulin so that insulin is adequately stored in the pancreas and released when glucose enters the blood stream.

Second, zinc improves cell health, making up a component of the enzymes necessary for insulin to bind to cells so that glucose can enter and be used as fuel. The process of insulin binding to the cell is what is referred to "insulin sensitivity" and means that the cell is receptive to insulin. Once insulin binds to the cell, it "opens the door" so that the glucose can enter. If the cell is resistant to insulin, glucose may stay in the blood stream, cause high blood sugar, and ultimately lead to fat gain.

Third, zinc has anti-inflammatory effects via its role in abolishing inflammatory markers such as C-reactive proteins. Zinc also helps get rid of substances that cause inflammation in cells, helping to preserve cell health and insulin sensitivity [12]. Chimienti *et al*. [13] discovered that the insulin storage and secretion properties of zinc are made possible by a zinc containing molecules called zinc transporter ZnT8 in the cell. ZnT8 is targeted by autoantibodies in 60% to 80% of new cases of type 1 diabetes, and about 3% of type 2 diabetic patients [14].

A 2009 study from Harvard Health looked at how zinc levels influence diabetes risk for women. The study looked at around 80,000 women over a period of 20 years and found that higher zinc levels were associated with a slightly reduced risk of type 2 diabetes [2]. In a study that reviewed 111 articles, the results showed that zinc plays an important role in β-cell function, insulin action,

glucose homeostasis and the pathogenesis of diabetes and its complications [15]. Zinc supplementation resulted in a significant reduction of plasma total cholesterol, LDL-c and TAG, while increasing HDL-c levels in patients with type-2 diabetes [16]. A study has indicated that zinc treatment significantly decreased body weight gain in lean G-K rats, and induced body weight reduction in overweight or obesed aged S-D rats. On the other hand, plasma leptin levels were significantly decreased in both aged S-D and G-K rats, but not in lean G-K rats. In contrast to plasma leptin levels, plasma adiponectin levels were significantly increased ($P < 0.001$) in aged, overweight S-D rats, but not in lean, diabetic G-K rats. Plasma adiponectin levels exhibited a tendency to be lower in aged, overweight S-D rats than in young G-K rats. These data were consistent with the concept that adiponectin metabolism is generally related inversely to the leptin metabolism in animals and human forms of obesity [17].

Calcium

Calcium is the most abundant mineral in the body and could help reduce diabetes risk by up to 33 % [2]. Calcium is an essential component of intracellular processes that occur within insulin responsive tissues like skeletal muscle and adipose tissue. A narrow range of calcium concentration is needed for optimal insulin mediated functioning. Levels that are out of this optimal range may contribute to peripheral insulin resistance [18]. When the body's calcium concentration is low, it will turn to the skeletal system for its calcium requirements, thereby weakening the bones. Many studies show an association between low calcium and vitamin D levels and decreased insulin sensitivity, but not all of them are conclusive. Supplements that combine both calcium and vitamin D may therefore help normalize blood sugar levels, decrease insulin resistance and risk of type 2 diabetes [18].

The exact mechanism by which calcium alters diabetes risk is unclear. However, abnormally low intracellular calcium due to low levels of vitamin D has been suggested. This hypothesis is supported by studies indicating that calcium is essential in normalizing glucose intolerance *in vivo* [19]. Another hypothesis also suggested that insulin secretion is a calcium dependent process. When blood glucose levels increase, the glucose is transported inside the cells with the help of GLUT-4 transporters and is converted to glucose-6-phosphate with the aid of glucokinase. This is further oxidized to yield increased ATP, which causes closure of potassium channels and hence depolarization of the cell membrane. Depolarization leads to an increased

calcium flux through calcium channels which causes docking of vesicles containing insulin to fuse with the cell membrane, culminating in insulin secretion by exocytosis [20].

Some studies have indicated that high doses of calcium may actually lead to a higher chance of getting type 2 diabetes, while others have reported its diabetic regulatory properties at moderate doses [2]. A total of 863 individuals between the ages 40-69 were included in a study, and none of them had diabetes at the start of the study. Aside from their serum calcium concentrations, participants had their insulin sensitivity and acute insulin response measured at baseline and then every few months. The development of diabetes or an impaired glucose tolerance (IGT) was determined from their most recent fasting and 2-hour post-prandial glucose levels and/or whether the patient started using anti-diabetic medications. The results of the study indicated that there was a relationship between serum calcium concentration and the development of diabetes or IGT, but this relationship was not linear. This was because increased risk for diabetes was most seen when patients had the highest levels of serum calcium (>2.5 mmol/L). Furthermore, researchers found a patient's calcium concentration to be unrelated to glucose and insulin secretion and insulin sensitivity. So, the study does not provide the evidence to suggest that a high calcium concentration causes type 2 diabetes. However, it can be classified as a risk factor [21].

Vanadium

Vanadium is a scarce metal that has been surprisingly demonstrated in few human and animal studies to be beneficial in diabetes management. However, the use of vanadium as a dietary supplement is highly controversial, as vanadium can be toxic at high doses [2]. The mechanism of action of vanadium in controlling diabetes involves inhibition of production of nitrogen oxide (NO), which delays the onset of type 1 diabetes [22]. This metal aids in the prevention of beta cell autoimmunity by assisting macrophages to produce NO free radicals. With the help of vanadyl complexes, macrophages produce NO free radicals, which are made by nitric oxide synthesase (iNOS), used against pathogens. A high concentration of NO is thought to cause the production of hydroxyl (OH) free radicals which causes damage to beta cells [22]. Another hypothesis also postulates that vanadyl complexes may regulate blood sugar at three possible sites. First, it inhibits the secretion of protein tyrosine phosphatases (PTPase). This enzyme is responsible for dephosphorylating tyrosine residues in proteins [23]. This causes the activation of

protein tyrosine kinases and phosphorylates insulin receptor substrates (IRS). The phosphorylated IRS then attracts various signaling proteins. Signals are sent through the cell initiating two cascades that lead to glucose transport and glycogen synthesis. A second target of vanadium is PTEN, which acts as a phosphatase. This prevents dephosphorylation and allows for cell signaling to occur by a similar pathway [23].

In the late 19th and early 20th centuries, before the 1922 discovery of insulin, French physicians found that administering sodium metavanadate (NaVO3) improved the health of patients with diabetes mellitus [24]. Vanadium, as vanadyl sulfate, is believed to regulate fasting blood sugar levels and improve receptor sensitivity to insulin [25]. Based on available research, vanadyl sulfate appears to be a useful intervention for type 2 diabetic individuals with insulin resistance. Vanadyl sulfate has been reported to be 6-10 times less toxic than vanadate [26]. In a single-blind, placebo-controlled study, the effect of vanadyl sulfate was examined in eight male and female subjects with type 2 diabetes. Treated subjects received 50 mg vanadyl sulfate twice daily for four weeks, followed by a four-week placebo phase. Modest improvements in fasting glucose and hepatic insulin resistance followed the treatment period and were sustained throughout the placebo period [25].

Selenium

Being an antioxidant, selenium is thought to offer some protection against chronic diseases, including diabetes [2]. The mineral is found naturally in foods like bread, meat and nuts. In some environments, selenium occurs in high concentrations in soil, which bio-accumulates in the inhabitants [27]. Selenium supplementation may have adverse effects in people who already received adequate selenium supply. Specifically, an increased risk of type 2 diabetes has been reported in individuals with high baseline selenium levels. However, this effect was restricted to males, suggesting the relationship between selenium and glucose homeostasis may be sexually dimorphic [28]. The difference between the beneficial and the harmful effects of selenium is very narrow; a little bit can be very good, while high dose can be harmful [29].

The mechanism by which moderate amount of selenium regulates blood glucose is not clear. Some studies hypothesized that the mineral is a mimetics (substances that mimic insulin). The insulin-like actions of selenium include stimulating glucose uptake and regulating metabolic processes such as glycolysis, gluconeogenesis, fatty acid synthesis and the pentose phosphate

pathway. Selenium does activate key proteins such as selenoprotein involved in the insulin-signal cascade necessary for different insulin-regulated events [30]. High doses of sodium selenate (0.1 to10 mM for 10 or 20 min) stimulated glucose uptake in isolated rat adipocytes through enhancing translocation of glucose transporters to plasma membrane, and activating serine/threonine kinases including p70 S6 kinase [31]. The theorized mechanism of how excess selenium could be pro-diabetic is that after a certain threshold of selenium intake (past the RDA, nearing the TUL), selenium builds up in pancreatic tissue [32] and exerts oxidative stress on beta-cells that secrete insulin [33]. This may be an issue of selenium being anti-diabetic acutely (via acting as an insulin-mimetic and aiding in glucose deposition) but over time damaging beta-cells and exerting the opposite effect and being pro-diabetic [30].

Several studies have demonstrated that selenium could play an important role in diabetes control. A 2012 study at Yeungnam University in Korea looked at the levels of selenium in the toe nails of around 6,000 men and women to assess any correlation between diabetes risk and selenium intake. The researchers found that in dietary levels of selenium intake, men and women had a reduced risk for type 2 diabetes. Individuals who took selenium supplements showed a higher reduction in risk for getting type 2 diabetes [2]. A study in France found that elderly men with higher selenium levels had a lower risk of later developing type 2 diabetes or impaired fasting glucose [34].

Omega-3 Fatty Acids

Omega-3 fatty acids are integral part of cell membranes throughout the body and affect the functions of the cell receptors in these membranes [35]. Foods high in Omega-3 include fish, vegetable oils, nuts (especially walnuts), flax seeds, flaxseed oil, and leafy vegetables [35]. Omega-3 fatty acids help reduce type 2 diabetes risk. Dietary supplements especially with fish oil are being used to treat the typical dyslipidemia associated with diabetes. While animal fats are high in saturated fats, fish oils are high in polyunsaturated fats, specifically omega-3 fatty acids [36].

Two mechanisms have been proposed for the hypoglycemic and antidiabetic effects of omega-3 fatty acids. The first is the insulin-sensitizing effect caused by omega 3 polyunsaturated fatty acid (n-3 PUFAs), which is based on Glucagon-like peptide-1 (GLP-1) secretion mediated by G-protein coupled receptor 120 (GPR120). Because this effect correlates strongly with the

intestinal GPR120 location, targeted delivery of n-3 PUFAs to the colon is essential for the most effective control of blood glucose level by n-3 PUFAs. The second is the insulin-sensitizing effect of n-3 PUFAs mediated by sterol regulatory element binding protein (SREBP) and peroxisome-proliferator-activated receptor (PPAR). The two hormone receptorsalter lipid metabolism and suppress inflammation, and thereby ameliorate insulin resistance [37].

Several studies show that omega-3 fatty acids play a huge role in blood glucose control. A case-cohort study of type 1 diabetes indicated that the intake of omega-3 fatty acids between the ages of 1 and 6 years was associated with a decreased risk of β cell autoimmunity [38]. A study by Virtanen *et al* [39] also revealed that increasing fish intake, containing omega-3 fatty acids, can also reduce the risk of type 2 diabetes in men. Omega-3 fatty acids, especially those derived from fatty fish like salmon, mackerel, or sardines, may have a wider health benefit than previously suspected. Of importance to people with diabetes is the finding by Hess-Fischl [36] that docosahexaenoic acid (DHA) may reduce the formation of harmful glucose metabolites linked to diabetic complications.

CONCLUSION

Several studies reviewed showed mineral deficiencies and, in some cases, over-dose of certain minerals may cause diabetes mellitus. Therefore, diabetics and nondiabetics are advised to ensure the right balance of minerals in the body with the assistance of qualified medical personnel.

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