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Review Article

The Significance and Importance of Elements in Diabetes Mellitus

Arun Kumar D[1], Revathy K[2], Dhananjayan R[3], Rajeswari S[4] and Swaminathan S[5]

[1]Senior Lab Technologist, [2]Junior Technical Officer, [3]Consultant, [4]Junior Technical Officer, [5]Senior Consultant and Head, Department of Biochemistry, Apollo Speciality Hospitals, Ayanambakkam, Chennai 600 095, India

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ABSTRACT

As of date, 104 Elements have been identified and 36 elements have been found to be essential for plant and animal growth and development. Human body requires about 10 Macro elements for structural growth and 6 trace metals are found to be essential for metabolism, all of which are interlinked to various types of Diabetes Mellitus (DM). Although trace elements constitute a minute part of human body, they are very essential for various enzyme activities. All enzymes will get activated only if metals are incorporated. Among various elements present in human body, Ca, Mg, P, Zn, Cu, Cr, Co, Mn, Se, and Fe play a significant role in controlling DM. Zinc is the trace element extensively studied in DM and reproduction. This review article is based on the various research findings done during the last 10 years and will certainly help research scholars to do further research in this field and to arrive at a set of laboratory investigations for elements linked to DM.

Key words: Elements, Ca, Mg, Zn, Cu, DM and T2DM

INTRODUCTION

Elements are basic ingredients of human body. Nitrogen, Sulphur, Oxygen, Hydrogen and Carbon form the organic compounds such as proteins, carbohydrates, fats and vitamins. Approximately 36 elements out of 104 identified so far are involved in human metabolic pathways serving as structural elements of skeleton and soft tissues and acts as factors regulating many physiological functions like blood coagulation, oxygen transport and enzyme activations. Macro elements are those present in body tissues at a level of IG / IG wet weight of the tissue. These include Chlorine (Cl), Phosphorus (P), Magnesium (Mg), Potassium (K), Sodium (Na) and Calcium (Ca). Micro elements refers to elements present in biological fluids at a concentration of less than 100 parts per million i.e <100µg/L. Some of the essential trace elements are Chromium (Cr), Zinc (Zn), Iodine (I), Cobalt (Co), Manganese (Mn), Copper (Cu), Molybdenum (Mo), Selenium (Se), Vanadium (V) and Iron (Fe). There are some elements present in body fluids which are toxic but which enters the human body as nuisance. These include Arsenic (As), Nickel (Ni), Tin (Sn), Mercury (Hg), Cadmium (Cd) and Lead (Pb). However, some of them shows beneficial effects.

Trace elements constitute a minute part of the living tissues and have various metabolic characteristics and functions. Trace elements participate in tissue and cellular and subcellular functions such as immune regulation by humoral and cellular mechanisms, nerve conduction, muscle contractions, membrane potential regulations, and mitochondrial activity and enzyme reactions. The status of micronutrients such as iron and vanadium is higher in Type 2diabetes (T2DM), whereas Cr, Co, I2, Fe, Se, Mn & Zn seem to be low in T2DM while Cu has no effect. Macro metals Ca & Mg play a major role in the development of T2DM. T2DM is the commonest major metabolic disease and is the most prevalent diseases worldwide. Its related morbidity is due to its micro and macro angiopathic complications. A definite lowering of serum Mg and Zn levels were significant in diabetic group. Decreased serum Zn levels in diabetes may be caused by an increase in urinary loss. These decreased levels of trace elements cause disturbances in glucose transport across cell membrane due to insufficient formation and secretion of insulin by pancreas which compromise in the antioxidant defense mechanisms [1]. There is accumulating evidence that the metabolism of several trace elements is altered in DM and that these nutrients might have specific roles in the pathogenesis and progress of this disease and its

***Corresponding Author Address:** Dr. S. Swaminathan, Senior Consultant and Head, Department of Biochemistry, Apollo Speciality Hospitals, No. 64, Vanagaram to Ambattur Main Road, Ayanambakkam, Chennai – 600 095. South India.*

complication. An association between micronutrients and periodontitis has also been suggested by preliminary studies. However, till date there is a lack of relevant clinical data. Imbalance of Zn, Cu and Fe levels in the serum can predispose an individual to the risk of developing periodontitis [2].

Increased production of Reactive Oxygen Species (ROS) necessitates higher requirements for the nutrients involved in antioxidant defenses. The levels of glutathione, catalase and Se are significantly lower in diabetic patients with periodontitis compared to healthy normal subjects [3]. Plasma Zn and Mg levels are significantly decreased in T2DM patients when compared with controls, suggesting that T2DM can result in changes in Zn and Mg levels [4]. Zn supplementation may have beneficial effects on glycemic control [5]. Participants with prediabetes have lower Zn levels than controls and Zn is significantly associated with beta cell function and insulin resistance. Zn supplementation in prediabetes could be a useful strategy in preventing progression to T2DM [6].

Zn dyshomeostasis is always related to certain disorders such as metabolic syndrome, diabetes and its diabetic complications. Zn deficiency is a common phenomenon in diabetic patients. Chronic low intake of Zn is associated with the increased risk of diabetes and impairs Zn metabolism and Zn supplementation may prevent the metabolic syndrome and diabetic complications [7]. Trace elements status are known to be altered in the diabetic state, although the factors affecting trace elements homeostasis condition are not well understood [8]. Elevated levels of Cu / Zn superoxide dismutase, a key enzyme in the metabolism of free oxygen radicals elicit a protective effect against diabetes-associated embryopathy [9].

The late organ complications in diabetic patients are associated with enhanced oxidation of low-density lipoproteins (LDL) and the role of vitamin and trace elements in this process are not clear [10]. DM is always characterized by hyperglycemia and is closely related to trace elements. Compared with normal pregnant women, the Cu contents in serum of pregnant women with Gestational Diabetes Mellitus (GDM) increased, but Zn contents had a decreasing trend [11]. High Se intake might affect expression and/or function of key regulators of glycolysis, gluconeogenesis, and lipogenesis. Future research is needed to find out if certain forms of Se metabolites in addition to selenoproteins and if mechanisms other than intracellular redox control mediate the diabetogenic effects of high Se intake [12].

Although there is a clear link between certain selenoproteins and glucose metabolism or insulin resistance, the relationship between Se and T2DM is undoubtedly complex [13]. No diabetogenic effect of a six-month supplementation with Se in a sample of elderly individuals with relatively low Se status was observed [14]. At dietary levels of intake, individuals with higher toe nail Se levels are at lower risk for T2DM. Further research is required to determine whether varying results in this study versus prior trials relate to differences in dose, source, statistical power, residual confounding factors, or underlying population risk [15]. Blood Pb, Hg and Cd have no significant relationship with diabetes in the general Korean population [16]. Cd exposure was not associated with increased risk of T2DM or Impaired Glucose Tolerance (IGT) [17].

No significant association between urinary Cd and diabetes in either gender was observed and environmental exposure to Cd may increase the risk of hypertension. Risk for diabetes in relation to Cd exposure remains uncertain in this exposed population [18]. Cd elevates fasting blood glucose levels in an animal model of subchronic Cd exposure before overt signs of renal dysfunction are evident. Cd reduces insulin levels and has direct cytotoxic effects on the pancreas and these findings indicate that Cd may be a factor in the development of some types of diabetes and they raise the possibility that Cd and diabetes-related hyperglycemia may act synergistically to damage the kidney [19].The striking dose-dependent links between markers of Cd exposure and of T2DM nephropathy highlight the need for further definitive research on the health effects of Cd in the presence of diabetes [20]. High dietary intake of heme iron was associated with an increased risk of developing T2DM in a Mediterranean population at high cardiovascular risk [21].

There is growing concern about the relationship between iron stores and the severity of T2DM. Poorly controlled patients with T2DM and people without diabetes of over 55 years of age are likely to be at a higher risk of developing hyperferritinaemia. Thus, regular assessments of serum ferritin is important for those who are at risk of hyperferritnaemia for prevention and an early intervention [22]. Both low and high serum ferritin (possibly reflecting depleted and excessive iron stores, respectively) along with high serum soluble Transferrin Receptor (sTfR) (reflecting reduced metabolically available iron) identify patients with T2DM and Coronary Artery

Disease(CAD) who have a poor prognosis [23]. The serum ferritin level was markedly higher in women with GDM than in normal pregnant women; therefore, high ferritin can be regarded as a significant risk factor for the development of GDM [24].

Imbalance of Zn, Cu and Fe levels in serum can predispose an individual to the risk of developing periodontitis [25]. Antagonistic interaction between Mo and Cu might be involved in the progress of diabetes complications [26]. Obesity is associated with alterations in maternal-fetal disposition of some essential trace elements and antioxidant enzyme status and that these alterations could pose a potential health risk for the mother as well as the fetus [27]. Altered maternal-fetal status of some essential trace elements in GDM patients could have deleterious influences on the health of the mother as well as the fetus and newborn [28].

High-dose oral Zn might enhance wound healing, although data regarding diabetes are lacking. Cr increases tissue sensitivity to insulin and tends to raise high-density lipoprotein (HDL) cholesterol and the HDL:LDL ratio. Se is involved in processes which protect the cell against oxidative damage by peroxides produced from lipid metabolism. An insulin-like effect has recently been attributed to V in experimental animals, a finding of potential interest to man. Current knowledge does not implicate Fe, I_2, Mn, Co, Ni, Si, F, Mo or Sn in the pathophysiology of diabetes. Appropriate trace element supplementation might prove beneficial in ameliorating some physiological deficiencies associated with diabetes and prevent or retard secondary complications. The potential roles of V, Cr and Se in diabetes constitute challenging areas for further experimental and clinical research [29].

Trace element disturbances are well known in T2DM and its associated complications. Serum Cu level was increased in T2DM patients with proteinuria while Fe was found to be elevated in T2DM compared to control groups. Zn and Mg were significantly low in proteinuria, T2DM with proteinuria, and T2DM compared to controls. Serum Cu showed strong positive association with albumin creatinine ratio (ACR) in T2DM with proteinuria as well as T2DM groups. Fe was positively and Zn was negatively associated with ACR in T2DM with proteinuria group. Mg was negatively linked with ACR in proteinuria, T2DM with proteinuria, and T2DM group. Trace elements metabolism were disturbed in T2DM with proteinuria group, thus considered to be the part of T2DM routine checkup and restricts the disease towards its progression [30].

Diabetics had higher Total Sialic Acid (TSA), Lipid-bound Sialic Acid (LSA), Fe, Mn, Fe/Zn and Cu/Zn levels, and lower Zn and Mg levels than those of controls. Although, Cu levels were higher, and Cr levels were lower in male diabetic patients, they were not different in female diabetic patients than in controls, suggesting that TSA, LSA and selected minerals have interactive connections with DM. There are also many sex-related positive or negative correlations between the altered parameters in diabetic patients. These parameters might be used as diagnostic indices in patients with DM [31]. The mean values of Zn, Mn and Cr were significantly reduced in blood and scalp-hair samples of diabetic patients as compared to control subjects of both genders. The urinary levels of these elements were found to be higher in the diabetic patients than in the age-matched healthy controls. In contrast, high mean values of Cu and Fe were detected in scalp hair and blood from patients versus the non-diabetic subjects, but the differences found in blood samples was not significant. These results are consistent with those obtained in other studies, confirming that deficiency and efficiency of some essential trace elements may play a role in the development of DM [32].

The mean values of K, Mg and Ca are significantly reduced, while Na level is higher in blood and scalp hair samples of hypertensive diabetic (HD) patients and non-hypertensive diabetic (NHD) patients as compared to control subjects of both genders, but level of K in the biological samples of NHD patient was found to be higher, but it was not significant. The urinary levels of these elements were found to be higher in both HD and NHD patients than in the age-matched healthy controls. These results are consistent with those obtained in other studies, confirming that deficiency and efficiency of some essential trace metals may play a role in the development of DM [33]. The mean values of Pb, Cd and As were significantly higher in scalp hair samples of smoker and non-smoker diabetic patients as compared to control subjects. The concentration of toxic elements was also high in blood and urine samples of DM patient but difference was more significant in smoker DM patients. These results are consistent with those obtained in other studies, confirming that toxic elements may play a role in the development of DM [34]. The disturbance in the Zn micronutrient and increased oxidative stress in T2DM may bring about insulin resistance and the creation of diabetic complications. The progression of DM may bring about perturbation in micronutrient metabolism and status [35].

The number of people with diabetes and pre-diabetes are exponentially increasing. Studies on humans have shown the beneficial effects of Zn supplementation in patients with diabetes as LDL-C showed distinct reduction in the Zn treated group. Studies have also shown a significant reduction in systolic pressure. This first comprehensive systematic review and meta-analysis on the effects of Zn supplementation in patients with diabetes demonstrates that Zn supplementation has beneficial effects on glycemic control and promotes healthy lipid parameters. Further studies are required to identify the exact biological mechanisms responsible for these results [36].

Several studies reveal changes in Zn metabolism in individuals with T2DM and controversies remain regarding the effect of Zn supplementation in the improvement of oxidative stress in these patients. Faced with the serious challenge of the metabolic disorders related to oxidative stress in diabetes along with the importance of antioxidant nutrients in the control of this disease, new studies may contribute to improve our understanding of the role played by Zn against oxidative stress and its connection with the prognosis of T2DM [37]. Chronic low-grade inflammation in T2DM can elicit changes in whole-body Zn metabolism. A study presents Zn supplementation increases cytokine gene expression in T2DM, and relationships found among Zn transporters, Metallothionein and Cytokines suggest close interactions between Zn homeostasis and inflammation [38].

No significant effects of Zn or α-linolenic acid (ALA) supplementation were observed on inflammatory marker concentrations or hold change in Zn transporter and metallothionein gene expression. Significant increases in plasma Zn concentrations were observed over time in the groups supplemented with Zn alone or combined with ALA. Associations among inflammatory cytokines and Zn transporter and metallothionein gene expression support an interrelationship between Zn homeostasis and inflammation in T2DM [39]. Expression of Zn transporters can be tissue/cell-type specific or ubiquitous. Zn transporters that are limited in tissue/cell distributions usually perform specialized tasks to satisfy biological processes in a given cell. For example, ZNT8 is mainly expressed in β-cells and functions to deliver Zn into granules for insulin maturation and secretion. Many other Zn transporters are also expressed in β-cells. Defects in these Zn transporters have been associated with abnormalities in insulin synthesis, maturation, and secretion and subsequent glucose metabolism [40].

Pancreatic β cells contain the highest amount of Zn among cells within the human body, and hence, the relationship between Zn and diabetes has been of great interest. To date, many studies of Zn and diabetes have been reported, including studies demonstrating that diabetic patients and mice have a decreased amount of Zn in the pancreas. Zn may counteract the deleterious effects of oxidative stress, which contributes to reduced insulin resistance, and may also protect pancreatic β cells from glucolipotoxicity [41]. Although it is well known that insulin granules contain high amounts of Zn, the physiological role of secreted Zn remains elusive. That SLC30A8 gene regulates hepatic insulin clearance and that genetic dysregulation of this system may play a role in the pathogenesis of T2DM [42].

Concentrations of fasting and postprandial blood glucose were significantly higher in the diabetic group than controls and the mean HbA1c% was also higher in cases. The mean serum Zn concentration in cases was found to be significantly lower than controls suggesting an inverse relationship between Glycosylated Hemoglobin(HbA1c) and serum Zn concentration in patients with T2DM, substantiated by regression analysis [43]. Zn plays an unidentified role as a novel second messenger that augments insulin activity. This previously unexplored concept would raise a whole new area of research into the pathophysiology of insulin resistance and introduce a new class of drug target with utility for diabetes pharmacotherapy [44]. T2DM can result in changes in Cu and Zn levels. However, it is difficult to draw any definite conclusion from this small study sample but may be suggested that estimation of both Cu and Zn is better to be considered in those cases [45].

The urinary levels of these elements were found to be higher in the diabetic patients than in the age-matched healthy controls. In contrast, high mean values of Cu and Fe were detected in scalp hair and blood from patients versus the non-diabetic subjects, but the differences found was not significant. These results are consistent with those obtained in other studies, confirming that deficiency and efficiency of some essential trace elements may play a role in the development of DM [46].The metabolism of several trace elements has been reported to alter in DM and these elements might have specific roles in the pathogenesis and progress of this disease. The alterations observed in serum levels of Cu and Mn was not significant among diabetic and normal

subjects. Glycemic status, duration of diabetes and age did not affect the trace elements concentrations[47] The results confirm that deficiency and efficiency of some essential trace elements may play a role in the development of DM [47].—**to delete this text only.**

The deficiencies of essential trace elements, Cr, Mn and Zn in biological samples of diabetic women, may play a role in the pathogenesis of DM and impacts on their neonates [48]. It is well established that both the deficiency and possible overload of mineral micronutrients have adverse health effects. It is also generally accepted that non-essential xenobiotics contribute to oxidative damage, which is considered as one of the principal factors in diabetes and its complications and that antagonistic interaction between Mo and Cu might be involved in the progress of diabetes complications [49]. Several studies have indicated that the deficiency and efficiency of some essential trace elements may play a role in the islet function and development of DM. Some toxic metals have also been shown to be elevated in biological samples of DM patients. Some heavy metals may play an important role in DM as environmental risk factors [50]. HbA1c levels were positively correlated with Cu and Cu/Zn ratio and inversely correlated with Zn and Mg. Patients with DM had altered metabolism of Cu, Zn and Mg and this may be related to increased values of HbA1c and impaired metabolism of these elements may contribute to the progression of DM and diabetic complications [51]. Severe neuropathy and glucose intolerance on total parenteral nutrition receiving currently recommended levels of chromium, were reversed by additional supplemental chromium. Chromium increases insulin binding to cells, insulin receptor number and activates insulin receptor kinase leading to increased insulin sensitivity. Additional studies are urgently needed to elucidate the mechanism of action of chromium and its role in the prevention and control of diabetes [52]. The mean value of Pb and Cd were significantly higher in serum of diabetic patients when compared with the control but there was no significant difference in the concentration of As. The serum concentration of Se was significantly lower in diabetic patients than in healthy control group. Also, the concentration of the toxic elements showed positive correlation with fasting plasma glucose and inverse correlation with serum Se. Increased toxic metals are associated with DM. Thus, these elements may play a role in the development and pathogenesis of DM. In addition, depressions in antioxidant concentration especially Se may further aggravate this effect [53]. The levels of Fe, Zn, and Cu in the aqueous humor and serum of diabetic patients were not found to be statistically significant when compared to non-diabetics. These results demonstrate that increased Cu content of the lens presumably has a greater association with the development of lens opacification in diabetics than Zn and Fe content [54].

CONCLUSIONS

This review article has brought into focus the research findings related to elements and their role in regulating T2DM during the last decade. Among the trace elements, zinc plays a prominent role highlighting further research about its role in intracellular metabolic pathways. Even some toxic metals have been identified as playing a major role in altering some metabolic pathways in T2DM. The contents of this article will be an eye opener to undertake further research linking the role of Hg, V, Cd, Ni and Sr to T2DM, and to finalize a list of laboratory investigations for the measurement of important elements as additional laboratory diagnostic tools for the diagnosis of all T2DM patients.

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