Yassmin *et al.*, Sudan Academy of Sciences Journal, No. 10 , 2015, 9-18
ISSN 1816-8272

Plasma Zinc Status in Patients with Type 2 Diabetes Mellitus

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Abstract

Molecular and cellular studies have demonstrated several roles for zinc (Zn) in insulin production and the consequent action of insulin on metabolism. Clinical and epidemiological studies suggest that reduced Zn status is associated with diabetes. The aim of the present study was to investigate the plasma levels of zinc in patients with type 2 diabetes mellitus and in healthy subjects in Sudan. The diabetic patients had no other systemic disease and were taking no medication that would interact with zinc metabolism. Zinc concentrations were measured by means of atomic absorption spectroscopy. Mean (±SD) plasma zinc in diabetic patients was 0.565 mg/dl ± 0.135, and in the healthy control was 0.846 mg/dl ±0.154. The normal range of plasma zinc is 0.8-1.5mg/dl. Fasting blood glucose was measured and it was significantly higher in diabetics than in non diabetic control subjects ($p < 0.001$). The results of this study showed that patients with diabetes mellitus had low plasma zinc concentrations. It is concluded that impaired metabolism of this element may contribute to the progression and development of diabetes mellitus, and Zinc may have supplementary benefits in the routine management of the disease, and could be feasible strategies favoring the life quality of those who have type 2 diabetes mellitus.

***Keywords*:** Plasma zinc, Diabetes mellius

Introduction

Diabetes mellitus (DM) is a disease with severe complications and major health/economic impacts. It is a leading cause of morbidity and mortality worldwide, with an estimated 346 million adults being affected in year 2011. WHO projects that diabetes death will increase by two thirds between 2008 and 2030 (WHO, 2012).

In Sudan diabetes is an increasingly important problem, being responsible for 10% of hospital admissions and mortality (Ahmed *et al*, 2000). Recently increase in incidence of diabetes mellitus has been observed especially among urbanized population indicating that diabetes mellitus is emerging as important health problem (Ahmed, 2001). The results of a small-scale study carried out in 1996 indicated that diabetes population in Sudan is at around one million, 90% of them have type 2 diabetes. It also showed a prevalence of 3.4% of type 2 diabetes mellitus (Elbagir *et al*, 1996). The disease needs more attention regarding

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metabolic control, since good control reduces the prevalence of diabetic complications (Elmahdi *et al*, 1991).

Interest in trace elements including zinc has been steadily increasing over the last 50 years. Trace elements are accepted as essential for optimum human health, because of their diverse metabolic characteristics and functions. They serve a variety of catalytic, structural and regulatory functions, in which they interact with macromolecules such as enzymes, pro-hormones, pre-secretory granules and biological membranes (Al-Awadi and Srikumar, 2000). The status of trace elements in diabetic patients is influenced by diet, drugs and to a large extent, environmental factors (Tadayon *et al*, 2012). There is an accumulating evidence that the metabolism of several trace elements is altered in diabetes mellitus (Hussain *et al*, 2009) and that deficiency and efficiency of some essential trace elements may play a role in the development of diabetes mellitus.

Zinc is involved in numerous metabolic pathways as a co-factor for more than 300 enzymes (Rink and Kirchner, 2000). It is involved in the synthesis, storage, secretion, and conformational integrity of insulin (Zargar *et al*, 1998). Insulin is produced by the beta cell of the pancreatic islets as a single chain peptide that is bent around itself and linked by two inter-chain disulfide bonds. This proinsulin is cleaved by the removal of an intracellular chain fragment known as the "C-peptide" to form two peptide chain (alpha and beta) molecules of 51 amino acids cross-linked to each other by inter-chain disulfide bonds. This is the insulin monomer. In the presence of zinc within the cell, insulin monomers assemble to a dimeric form for storage and secretion as the zinc crystal. Lower levels of Zn may affect the ability of pancreatic islet cells to produce and secrete insulin, such as in type-2 diabetes (Chausmer, 1998). In subjects with type-2 DM with low Zn intake, the risk of coronary heart disease increases by a factor of two to four times and is a major cause of mortality among diabetic patients (Singh *et al*, 1998; Kazi *et al*, 2008). It has been suggested that abnormal Zinc metabolism may play a role in the pathogenesis of diabetes and some of its complication. Several of the complications of diabetes may be related to increased intracellular oxidants and free radicals associated with decreases in intracellular Zn and in Zn dependent antioxidant enzymes (Jayawardena *et al*, 2012; Chen *et al* 2009; DiSilvestro, 2000). Reduced zinc concentrations in plasma in type 2 diabetes patients suggest an elevated loss of this mineral in urine, resulting from hyperglycemia and polyuria, which is not compensated by increased intestinal absorption, and reduction in intestinal excretion of this trace element (Lima *et al*, 2011).

Several investigators have shown the perturbation of zinc metabolism in diabetics (Golik *et al*, 1993; Kinlaw *et al*, 1983). It has been suggested that hyperzincuria and impaired absorption are major causes of zinc deficiency among diabetic patients (Cunningham *et al*, 1994).

Genome wide association studies have identified the islet-restricted zinc transporter ZnT8 as a likely player in the control of insulin secretion and the risk of developing type 2 diabetes. These results also reinforce the view that this transporter represents an exciting therapeutic target for intervention in type 2 diabetes mellitus (Guy, 2010).

ISSN 1816-8272

In the present study, zinc plasma levels were measured in patients with type 2 diabetes mellitus and the influence of duration of diabetes on concentration of this element was determined. The primary aim was to ascertain whether or not patients with type 2 diabetes mellitus had a zinc deficiency, as zinc has been implicated in the pathogenesis of insulin resistance.

Materials and Methods

One hundred Sudanese diabetic patients of both sexes participated in this study; all patients are of type 2 diabetes mellitus, and were ≥ 40 years old. They had no other systemic disease and were taking no medication that would interact with zinc metabolism. Other 40 healthy subjects of matching age were also included to serve as control. All patients were seen at Gaber Abu Eliez medical center. Assessments were made by medical doctors. Two milliliters of venous fasting blood were aseptically collected in heparinized blood collection tubes (Becton Dickinson, #6480, Lot.4F107, USA) from each diabetic patient. The plasma was aspirated into sterile cryo-vials and was stored at –70 0C°. Also over night blood sample for the same patients were taken in tubes with anticoagulant (Sodium fluoride + oxalate) and plasma were analyzed immediately for glucose level using glucose oxidase, peroxidase and aminophenazone principle, by enzymatic – spectrophotometric (Tinder, 1969; Tietz,1991). Zinc was measured by a modified atomic absorption photometry method (Varian AA 220 Flame Atomic Absorption Spectrometer) suggested by Burtis and Ashwood, (1994). The spectral lines used for determination was 213.9 nm. Plasma samples were diluted five times with double distilled water just before sample measurement. The calibration graph used for Zn measurement was constructed applying normal aqueous standards. The normal range of plasma zinc is 0.8-1.5 mg/dl).

Statistical analysis was performed using the epi info 2006 (CDC/ WHO free shaware), A value of $P < 0.05$ was considered as significant in all statistical analyses.

Results

Hundred patients with type 2 diabetes mellitus (33 men, 67 women; mean age 57.6 ± 9.2 years) and 40 healthy non-diabetic subjects of matching age (46.9±9.6 years) comprised the study group. The mean duration of diabetes was 7.5 ± 6.3 years. Demographic information for patients with type 2 diabetes mellitus is shown in Table (1).

As expected, the fasting blood glucose levels were significantly higher in the diabetics than in the control group 196.1 mg/dl and 100.4 mg/dl respectively. Analysis of the data showed a statistically significant difference in plasma zinc levels between diabetic patients and healthy controls where diabetics exhibit low values of zinc (0.565±0.135 mg/dl) compared with the control group (0.846±0.145 mg/dl) ($p < 0.001$) Table (2).

Table (3) shows the plasma zinc concentration in diabetic patients according to the duration of the disease. Zinc levels were found to be highly correlated to the duration of the disease ($p < 0.001$); where zinc concentration was dependent on

ISSN 1816-8272

the time of diagnosis, it is elevated at the beginning of the manifestation of the disease, and reduced in later periods (>10 years).
Subdividing the data according to sex showed a significant difference in plasma zinc levels between males (0.591 mg/dl) and females (0.552 mg/dl) ($p < 0.001$). Also mean plasma Zn concentration are highly correlated to age of diabetic patients ($p < 0.001$).

Discussion

Many studies have been conducted to explore body zinc status in patients with type 2 DM, however, conclusion still remains controversial (Winokan *et al*, 2010). Our study showed plasma Zn values of 0.846 mg/dl in the control subjects, while values of o.565 mg/dl were found in the plasma of type 2 diabetic patients. The significant reduction ($p < 0.001$) may indicate that diabetes mellitus may indeed reduce the level of plasma zinc in patients suffering from type 2 diabetes. These finding are in agreement with findings reported by other workers (Zargar *et al*, 1998; Walter *et al*, 1991). Low levels of plasma zinc from type 2 diabetes mellitus patients compared to control group were also determined by Marjani (2005). Another study in 20 age/sex matched controls and 30 diabetic patients, showed that the serum Zn was approximately 40% lower in the diabetes group ($p < 0.001$) (Garg *et al*, 1994). Kazi *et al* (2008) also reported low levels of Zn in whole blood and scalp hair of diabetic patients. Hussain *et al* (2009) also reported significantly reduced mean (±SD) Zn levels in blood samples of diabetic patients as compared to the control subjects ($p < 0.05$). Other studies concluded that impaired metabolism of Zn may contribute to the progression of DM and diabetic complications (Tadayon *et al*, 2012; Viktorinova *et al*, 2009).
It has been postulated that low zinc level in diabetic patients may be due to excessive urinary output resulting from hyperglycemia and polyuria, especially in patients with diabetic nephropathy, gastrointestinal malabsorption or genetic factors or signs of infection during which zinc will act as a defense mechanism (Chausmer, 1998; Kinlaw *et al*, 1983).
Few studies have been conducted on the effects of zinc supplementation on hyperglycemia of diabetics and their results are inconsistent. Zinc supplementation has improved fasting insulin level and fasting glucose in genetically obese mice models (Simon and Taylor, 2001). An improved fasting glucose level up to 30% in patients with cirrhosis through supplementation of zinc for 2 months has been reported (Marchesini *et al*, 1998). Supplementation of 50 mg zinc in type 2 diabetics showed a decrease in HbA1c concentration (Hyun-Mee and Jin-Sook, 2008). Sun *et al* (2009) reported that higher zinc intake may be associated with a slightly lower risk of type 2 diabetes in women and Zheng *et al*, (2008) found that diabetes is strongly associated with Zn deficiency. Hence, zinc supplementation may provide a significant protection against diabetes-induced complications for diabetic individuals. Other studies showed that zinc supplementation improved glycemic control (Gunasekara *et al*, 2011) and desirable changes in lipid profile as well as improvement in kidney functions were reported (El-Ashmony *et al*, 2012). Jayawardena (2012) reported that Zinc supplementation causes significant reduction in FBG, PPBG and HbA1c in

ISSN 1816-8272

patients with type-2 diabetes. In other studies zinc supplementation in diabetic patients shows antioxidant properties (Roussel *et al*, 2003; Anderson *et al*, 2001). Previous investigators have hypothesized that zinc enhances tyrosine kinase phosphorylation in the insulin signal transduction from in vitro studies (Simon and Taylor, 2001). Also serum insulin and C-peptide were significantly increased after zinc supplementation in patients with more than 4 years history of diabetes (Hyun-Mee and Jin-Sook, 2008).

Table 1. Demographic informaion for patients with type 2 diabetes mellitus

Group	Number of patients	Mean ±SD
Age (years)	100	Mean ±SD 57.6±9.2
Sex Female/Male	67/33	Ratio 2:1
Age Groups ≤ 50 > 50	 28 72	 28% 72%
Diabetes mellitus duration (1-10 years) (>10 years)	 75 25	75% 25%
Glucose levels ≤ 110 mg/dl > 110 mg/dl	 12 88	12% 88%

Table 2. Plasma Zn concentration and fasting blood glucose levels in diabetic patients and healthy control

Group	Number of patients	Mean Fasting blood glucose concentration (mg/dl)	Mean Zn concentration (mg/dl) Normal range (0.8-1.5 mg/dl)
Diabetics	100	196.1±62.5	0.565±0.135
Control	40	100.4±2.96	0.846±0.145

* Significant effect fasting blood glucose $p < 0.001$.

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Table 3. Plasma zinc concentration in diabetic patients according to duration of diabetes.

Duration of disease (years)	Number of patients	Mean Zn concentrations (mg/dl) Normal range (0.8-1.5 mg/dl)
1-10	75	0.571±0.175
> 10	25	0.529±0.135

* Significant effect of duration $p < 0.001$.

The results also showed that zinc concentration in type 2 diabetic patients was dependent on the time of diagnosis; it is elevated at the beginning of the manifestation of the disease, and reduced in later periods. This could be due to the loss of Zn from urine caused by chronic complications of diabetes mellitus, which may occur between 5 and 10 years after the onset of the disease. However, the excretion of zinc in urine was not determined, which is a limitation of this study.

It is concluded that, plasma zinc levels of the diabetic patients were noticeably lower compared to those of healthy controls and were dependent of the duration of the disease. Zinc may have supplementary benefits in the routine management of type 2 DM, and could be a feasible strategy favoring the life quality of those who have risk factors for other diseases in addition to diabetes, however, long term clinical studies establishing safety (lack of toxicity) and efficacy are required before any recommendations can be made for people with diabetes.

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ISSN 1816-8272

مستوى الزنك في بلازما مرضى السكري من النوع الثانى في السودان

ياسمين ابراهيم حلمى[1] ومريم خالد حسن[1]

مستخلص البحث

أظهرت الدراسات الجزيئية والخلوية عدة أدوار للزنك (Zn) في إنتاج الأنسولين وتاثيره على عملية التمثيل الغذائي للسكريات. كما تشير الدراسات السريرية والوبائية إلى ارتباط إنخفاض مستوى الزنك العام والإصابة بداء السكري. يتناول البحث قياس مستوى الزنك في بلازما المرضى بداء السكري من النوع الثانى والأشخاص الأصحاء في السودان. قيست تركيزات الزنك عن طريق الإمتصاص الذري الطيفي حيث أظهرت النتائج أن مستويات الزنك في بلازما مرضى السكري 0.565 ±0.135 ملغ/دل، بينما التركيز عند الأصحاء 0.846 ± 0.154 ملغ / دل. كما أوضحت الدراسة أن هنالك علاقة عكسية واضحة بين مدة مرض السكري ومستوى تركيز الزنك لدى مرضى السكرى من النوع الثانى. تم قياس مستوى السكر في الدم، وكان أعلى كثيراً لدى مرضى السكري مما كان عليه في الأشخاص الأصحاء.

خلصت الدراسة الى أن قلة التركيز وضعف التمثيل الغذائي لهذا العنصر لدى المرضى الذين يعانون من داء السكري قد تؤدى الى تطور المرض، عليه قد يكون لتناول الزنك كمكمل غذائي دور فاعل فى إحتواء مضاعفات هذا المرض.

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ISSN 1816-8272