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The Relationship between Zinc, Glycemic Control and Microvascular Complications of Diabetes Mellitus

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ABSTRACT

Background: Zinc is the second most abundant trace element in human body. The relationship between zinc and insulin is well known. Zinc is involved in the synthesis, storage and release of insulin and zinc deficiency may be associated with different metabolic disorders such as diabetes mellitus (DM). The aim of this study was to evaluate the serum zinc level and its correlation with glycemic control and microvascular complications in diabetic patients.

Methods: In this cross-sectional study, 128 cases of type 2 DM, 30-60 years of age were randomly selected on the basis of clinical history. Zinc level, HbA1c and urine micro albumin were measured. The Michigan Neuropathy Screening Instrument (MNSI) was used for evaluation of distal neuropathy.

Results: The subjects had mean age of 52.2±7.5 years old. Mean duration of DM was 8.3±7.4 years, mean HbA1c was 7.7±1.8% and mean zinc level was 101.5±26.5 µg/dL. There was a significant correlation between zinc and score of neuropathy (p=0.03). A subtle reduction in plasma zinc level was observed among patients with urine microalbumin ≥30 mg (96.0±14.9) in comparison to patients with urine microalbumin <30 mg (103.1±29.2) (p=0.09). By multiple regression analysis, after adjustment for age, BMI, sex and duration of diabetes, no significant association was noted between zinc level and HbA1c.

Conclusion: It was shown that plasma zinc concentration may have association with complications of type 2 DM such as neuropathy. This correlation was significant even in normal zinc level that should be considered by public health authorities.

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Introduction

Diabetes Mellitus (DM) is one of the most common health problems in developing countries resulting in morbidity and mortality. DM is a disorder of carbohydrate metabolism with heterogeneous characteristics by absolute or relative insulin deficiency and insulin resistance (1). International Diabetes Federation in their 5th edition of Diabetes Atlas estimated that the population of diabetic patients rose from 366 million in 2011 to 552 million by 2030 (2). Zinc (Zn) is the second most abundant trace element in the human body and is an important nutrient and cofactor of numerous enzymes and transcription factors (3).

It has been known for decades that a physicochemical relationship exists between insulin and zinc. Abnormalities in Zn homeostasis, such as its deficiency, may be associated with various chronic diseases and can also promote the progression of diabetes (4). Approximately, 10 to 40 percent of dietary Zn is absorbed in the small bowel; the presence of phytate and fiber in the diet that bind to Zn, inhibit its absorption. The Zn effect in homeostasis, immune responses, oxidative stress, apoptosis, and aging is well known (5).

Zn is involved in the synthesis, storage and release of insulin. It affects insulin production and secretion by pancreas, therefore Zn deficiency may lead to the development of type 2 DM (6). One of the causes of β cell loss in the pancreas of diabetic patients is the presence of Human Islet Amyloid Poly Peptide (HIAPP); Zn significantly inhibits fibrillogenesis of this factor and has been shown to prevent HIAPP mediated β cell loss (7). Many experimental and clinical trials have documented the relationship between Zn deficiency and glucose intolerance, diabetes mellitus, insulin resistance, atherosclerosis and coronary artery disease (8).

There are some studies which show antioxidant effect of Zn supplementation in diabetic patients (8). Also some studies delineated the antioxidant effect of Zn supplementation on the micro vascular complications of DM (9-11). The present study was undertaken to evaluate serum Zn level and to find out the correlation between serum Zn concentration and glycemic control and micro vascular complications in patients with type 2 DM.

Materials and Methods

The present study is a cross-sectional study undertaken on known cases of type 2 DM in the Motahari Diabetes Clinic from June 2014 to March 2015. After obtaining approval from Institutional Human Ethics Committee of Shiraz University of Medical Science (code number 92-01-01, 6767), 128 patients were selected randomly. All the study steps were performed in accordance with the Helsinki Declaration. All cases were between 30 and 60 years of age and selected irrespective of sex and socioeconomic status. Patients suffering from end stage renal insufficiency, liver disease, inflammatory bowel disease, sickle cell anemia and patients on Zn supplementation were excluded from the study.

At first, all individuals signed consent form. Questionaries' form was completed for each individual including his (her) diabetes history, anthropometric data and drug history. Weight and height were measured by a physician. Weight was measured with a standard scale to the nearest 0.1 kg (Seca, Germany), with the participant wearing light clothing and no shoes. Height was measured to the nearest 0.5 cm with a wall-mounted meter with the participant standing without shoes.

Body mass index (BMI) was calculated by dividing weight (in kilogram) by height square (in m^2). Waist circumference measurement was taken midway between the tenth rib and the iliac crest while standing and was recorded to the nearest centimeters. Blood pressure was measured twice by a physician. Briefly, it was measured with a manual sphygmomanometer (Rossmax Medical, Japan) in the right arm in the sitting position after resting for 5 minutes. Participants were recommended to avoid alcohol, cigarette smoking, caffeinated beverages, and exercise for at least 30 min before their blood pressure measurement.

The Michigan Neuropathy Screening Instrument (MNSI) was used for evaluation of distal symmetric polyneuropathy in these subjects (12). It comprised two parts including history and physical assessment. The history was a simple tool to assess subjective symptoms. The participants were asked to answer 15 questions. Responses were added to obtain the total score. A "yes" response to the items was counted as one point for each item and a "no" response on items 7, and 13 counted as 1 point.

Physical assessment was done by a trained physician considering the appearance of feet, ulceration, ankle reflexes, vibration perception at great toes, and monofilament. Possible obtainable scores varied between 0 and 1 for each item. Appearance of feet was evaluated by the presence of deformities, dry skin, callus, infection, and fissure. Deformity was diagnosed, if any of the following conditions was present: flat foot, hammer toes, overlapping toes, hallux valgus, joint subluxation, prominent metatarsal heads, medial convexity (Charcot foot), and amputation. All assessments were done in a room with the temperature around 30°C.

The ankle reflexes were examined using an appropriate reflex hammer. The monofilament was applied based on the protocol provided by Michigan Diabetes Research and Training Center. The 10-g monofilament was applied for ten times on each foot, and a "yes" response was indicative of the filament sensation. Eight correct responses out of 10 applications were considered as normal; 1-7 correct responses as reduced sensation, and no correct answers as absent sensation (12). All diabetic patients were examined by ophthalmologist for evaluation of diabetic retinopathy. Then they were referred to the Endocrinology and Metabolism Research Center Laboratory after 12 hours of fasting. Under

all aseptic and antiseptic conditions, 5 mL of blood sample was collected from a suitable peripheral vein.

Serum Zn was measured by colorimetric methods using kits supplied by LTA srl Company (Italy), Hemoglobin A1c (HbA1c) by ion exchange resin method, blood glucose by Glucose Oxidase/ Peroxidase method, blood urea, triglyceride, cholesterol, HDL and LDL cholesterol by modified Berthelot method, and creatinine by alkaline picrate method. Microalbumin in spot urine was measured by immunoturbidimetric assay (Microalbumin, Randox Laboratories Ltd., Crumlin, United Kingdom) using an autoanalyser (COBAS Mira S, Roche Diagnostics GmbH, Mannheim, Germany). Statistical analysis of the data was performed using SPSS Software (version 22, Chicago, IL, USA). Anthropometric data was presented as mean±SD and differences were detected by Student t-test or ANOVA. Correlation between Zn level and other parameters was analyzed by Pearson Correlation and Multiple Regression analysis. A P value of less than 0.05 was considered statistically significant.

Results

In our study, out of the 128 cases (mean age: 52.24±7.55 years), 37 were males and 91 were females. Females had a mean age of 51.14±7.03 years, whereas males had a mean age of 54.95±8.18 years (p=0.009). The mean BMI was 27.51±4.2 kg/m^2. The mean duration of diabetes was 8.3±7.4 years. Mean HbA1c level was7.7±1.8%, mean systolic blood pressure was 123.9±4.7 mmHg and mean diastolic blood pressure was 75±3.8 mmHg. The comparability of study groups between males and females with respect to baseline characteristics such as age, weight, height, waist circumference, BMI, duration of DM, systolic blood pressure and diastolic blood pressure are shown in Table 1.

The mean biochemical marker levels in males and females were shown in Table 2. There was a significant difference between males and females with respect to variables such as age, height, duration of DM, BMI, HbA1c, urine microalbumin, HDL, BUN, and creatinine level (p<0.05). But there was no significant difference in Zn level between males and females (p=0.09). Of all subjects, 97 (75.8%) had normal Zn level (70-120 µg/dL), 6 (4.7%) had Zn deficiency (Zn level below 70 µg/dL), and 25 (19.5%) had Zn level above 120 µg/dL. From 6 diabetic patients with Zn deficiency, 4 patients were female and 2 were male; four of them had HbA1c≤7.5%, two had urine microalbumin≥30, and five subjects had BMI≥25 kg/m^2.

Table 3 shows correlation between anthropometric and biochemical markers with Zn level. No significant association was found between Zn levels and age, weight, height, BMI, and duration of DM. We detected positive correlation between Zn level and total and LDL cholesterol (R=0.21, 0.19 and p=0.02, 0.03 respectively). In subgroup analysis,

Table 1: Baseline characteristics of the study groups.

Variable	Female	Male	*p* value	95% CI
Age (y/o)	51.1±7.0	54.9±8.1	0.009	0.9, 6.6
Weight (Kg)	70.2±11.2	70.9±9.1	0.7	-3.3,4.8
Height (cm)	156.4±7.2	169.3±8.4	<0.001	9.8,15.7
Waist Circumference (cm)	95.5±9.9	92.9±9.1	0.1	-6.3,1.2
BMI (Kg/m^2)	28.7±4.9	24.8±3.5	<0.001	-5.6,-2.1
Years of DM	7.2±6.1	10.9±9.5	0.03	0.2,7.1
Systolic BP (mmHg)	122±4	130±6	0.5	-19.6,35.7
Diastolic BP (mmHg)	73±4	82±3	0.05	-0.2,17.5

BMI: Body Mass Index; BP: Blood pressure; DM: diabetes mellitus.

Table 2: Biochemical characteristics of diabetic subjects.

Variable	Female	Male	*p* value	95% CI
HbA1c	7.36±1.57	8.17±1.65	0.01	-1.4,-0.1
Urine Micro albumin	18.6±49.1	267.2±531.0	<0.001	-437.1,-60.0
Triglyceride	134.9±57.6	140.2±60.6	0.6	-28.6,18.1
Cholesterol	170.0±32.9	162.0±35.2	0.2	-5.4,21.4
HDL	44.5±11.3	36.7±8.3	<0.001	3.4,11.9
LDL	69.7±21.4	67.3±21.0	0.5	-6.0,11.0
BUN	11.4±3.2	15.2±.9	0.01	-6.5,-0.8
Creatinine	1.01±0.10	1.38±0.87	0.02	-0.06,-0.6
Zinc	98.3±20.8	109.6±36.2	0.09	-24.6,2.0

HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; BUN: Blood Urea Nitrogen.

Table 3: Correlation between zinc level and anthropometric and biochemical markers in the study subjects (Spearman Analysis).

Analysis	Age	Weight	Height	BMI	Waist circum-ference	Duration of DM	Tri-glycer-ide	Cho-les-terol	LDL	HDL	HbA1c	Urine Microal-bumin
(Correlation coefficient)	0.13	-0.07	0.07	-0.14	-0.05	-0.10	0.18	0.21	0.19	0.02	0.056	0.009
p value	0.13	0.44	0.39	0.10	0.54	0.27	0.03	0.02	0.03	0.78	0.54	0.92

LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; BMI: Body Mass Index.

Table 4: Mean zinc level in study subjects with and without diabetic microvascular complications.

Analysis	Nephropathy			Retinopathy	
	Subjects with microalbumin <30 mg (88)	Subjects with microalbumin 30-300 mg (22)	Subjects with microalbumin >300 mg (7)	Subjects with retinopathy (27)	Subjects without retinoopathy (93)
Zinc Level	103±29.4	98.3±14.0	91.4±18.4	101.2±19.8	101.6±28.2
p value		0.45 (ANOVA)			0.9

Table 5: Association between zinc level and HbA1c (model adjusted for age, sex, BMI, and duration of DM).

	β (unstandardized coefficient)±SE	*p* value	95% CI
Sex	0.139±0.368	0.17	-0.22,1.23
BMI	-0.164±0.034	0.10	-0.12.0.01
Duration of DM	0.005±0.021	0.96	-0.04, 0.04
Zinc	-0.04±0.007	0.66	-0.01,0.01

Adjusted R Square: 0.02. BMI: Body Mass Index; DM: diabetes mellitus.

this association was significant only in females (r: 0.290, 0.261 and p=0.007, 0.015 for total and LDL cholesterol) and not in males (p=0.37, and p=0.35)

We did not find any significant association between Zn level and HbA1c. We divided our subjects to two groups with HbA1c ≤7.5 and HbA1c>7.5 and compared Zn level among them (99.2±22.7 and 104.6±30.7, respectively) (p=0.2). Also we found that 50th percentile of Zn level in our subjects was 96.8. We compared HbA1c in patients with Zn level of below 50th percentile and above 50th percentile that was 7.6±1.7 and 7.5±1.5 without any significant difference (p=0.8). Table 4 demonstrates mean Zn level in subjects with and without microvascular complications.

In this study, the individuals had neuropathy mean score of 6.15±3.68 according to MNSI and we found significant correlation between Zn level and score of neuropathy (R=-0.20, p=0.03). By regression analysis we evaluated the association between Zn level and HbA1c with adjusting for age, sex, BMI and duration of DM (Table 5). This model showed that age, gender, body mass index, duration of DM and Zn level predicted only 20% of change in HbA1c and any of them has not significant effect on control of DM.

Discussion

DM as a common health problem with morbidity and mortality and as a disorder of carbohydrate metabolism can be associated with Zn deficiency (13). Trace elements are required for growth and maintenance of life and health. Deficiency or insufficiency of such nutrients causes a functional impairment or can result in various diseases. The clinical significance of trace elements such as Zn, Cu, Cr, Mn and Mg in relation to DM remains controversial and there are many unanswered questions (14). Between the trace elements, Zn is the most particular especially in patients living with DM (15). The human body does not have any storage of Zn, so Zn level is absolutely dependent to dietary intake. According to a systematic analysis based on World Health Organization growth standards, about 17.3% of the world's population is at risk of inadequate zinc intake (16).

The prevalence of Zn deficiency in our country is from 7.9% in 3-18 years old children (17) to 13.6% in morbidly obese patients (18). The relationship between Zn and metabolic diseases (insulin resistance, metabolic syndrome and diabetes) is well known; because the presence of Zn is required for insulin synthesis and secretion from pancreatic β cell and also this trace element is important in stabilization of insulin hexamers. On the other hand, its anti-oxidative properties may delay progression

of insulin resistance and diabetes.

Kazi *et al*. showed that the mean values of Zn significantly reduced in blood and scalp-hair samples of diabetic patients as compared to control subjects of both genders (p<0.001). The urinary levels of these elements were found to be higher in these patients than in the age-matched healthy controls (14). Marchesini *et al*. explained another source for zinc depletion in diabetic patients. He explained that zinc deficiency seen in the diabetic population is due to the low gastrointestinal absorption and high urinary excretion of zinc in diabetic patients (19).

It seems that total body Zn deficiency in diabetic patients may be due to either increased urinary loss of Zn or decreased intestinal absorption of Zn (20). In our study, the level of Zn concentrations were in normal range in type2 DM patients and only 4.7% of our diabetic subjects were Zn deficient; although our study didn't include control group and we did not compare Zn level in diabetic and normal population. Results of our investigation on Iranian diabetic patients were consistent with the other research in Iran by Mashhadi *et al*. (21), and Dehghani *et al*. (17), that showed low level of Zn deficiency in normal population and some other Iranian studies that did not find any significant difference in Zn level between diabetic and non-diabetic subjects (22, 23).

Deghani *et al*. concluded that Zn deficiency in Shiraz is not as prevalent as other areas of Iran. It seems that pattern of nutrition and Zn level in the soil can predict blood level of this trace element in the population (17). We found that glycemic index of diabetic patients, which was measured by HbA1c, has not been influenced by Zn level. These results are similar to those of Zargar *et al*. (24) that did not find any significant relationship between Zn level and fasting blood glucose in diabetic subjects.

Some studies have practiced the relationship between Zn and glycemic index. Saharia *et al*. found an inverse relationship between Zn level and glycated hemoglobin in newly diagnosed diabetic patients (25). Bandeira and coworkers showed that increased level of Zn was associated with decrease in HbA1c (26). Also in a research by Luo *et al*. in China, an inverse relationship between Zn level and HbA1c was defined (27). In our study, only 4.7% of all subjects were Zn deficient and mean Zn level was 101.56 µg/dL. In the study of Saharia and Bandeira, the mean serum Zn level was 79.85 µg/dL (25) and 83.3 µg/dL (26) in diabetic patients. Mean Zn level in our subjects was significantly greater than them (p<0.001). This may be the probable cause of the lack of association between Zn level and HbA1c in our study.

The role of oxidative stress in the development of diabetic microvascular complications is well known. Also the antioxidative effect of Zn is well defined; as Zn induces the clearance of free radicals and inhibits lipid peroxidation induced cell damage (28). These findings determine the impression of Zn deficiency in diabetic microvascular complications. Although the mean Zn level in this cross sectional study was in normal range, we found the significant effect of Zn on diabetic neuropathy. Also we showed a subtle elevation in plasma zinc level among patients with urine microalbumin <30 mg in comparison to patients with urine microalbumin ≥30 mg.

Luo and coworkers also found that lower serum Zn level in diabetic patients was related to higher prevalence of diabetic microvascular complications, and also lower Zn level represented as an independent risk factor for diabetic neuropathy (27). Hayee and associates found lower serum Zn level in diabetic patients with neuropathy and improvement in this complication with Zn supplementation (29). The negative relationship between Zn level and lipid peroxidation can explain the association between lower Zn level and diabetic neuropathy (30). Also Zn can protect the diabetic patients from neuropathy via regulation of metallothionein expression and inhibition of oxidative stress (30).

Conclusion

This cross sectional study showed that Zn concentration was in normal range in our diabetic patients and glycemic index (HbA1c) has not been influenced by Zn level, but we found an inverse association between Zn level and diabetic neuropathy even in normal range of Zn level. The conflicts between results of this and other investigations may be explained by the fact that 95.3% of our study subjects had normal Zn level. Although the authors feel that further population-based research and controlled trials are required to clarify these findings in this province of Iran, the significant burden of neuropathy for diabetic patients and inverse relationship between Zn level and this complication should be of concern for public health system.

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Conflict of Interest

None declared.

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