Original Article

An observational study to estimate the level of essential trace elements and its implications in type 2 diabetes mellitus patients

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Abstract

Background and Objectives: Insulin action of reducing blood glucose has been found to be enhanced by trace elements. **Material and Methods:** This was a cross sectional study including 150 patients with Type 2 Diabetes Mellitus (T2DM) and 50 controls. Serum concentrations of zinc, copper, chromium, selenium and magnesium was measured by colorimetric kit. Fasting Blood Glucose and Glycated Haemoglobin (HbA1c) were assayed using the standard kit. **Results:** Out of 150 patients, 85.4% ($n = 128$) of the cases had uncontrolled blood sugar with HbA1c ≥7 and only 14.6% ($n = 22$) had good control of blood sugar with HbA1c <7%. Hypertension (42%) and hypothyroidism (14%) were the most commonly associated comorbidities among patients with T2DM. Following percentage of diabetic patients had complications such as peripheral neuropathy (45.3%), diabetic retinopathy (36.7%), coronary artery disease (20.7%), diabetic nephropathy (17.3%), peripheral vascular disease (8.7%), and cerebrovascular accident (6%) respectively. The mean level of zinc, copper, selenium and magnesium was significantly lower in patients with T2DM than the control cases (62.89 vs. 74.95 μg/dL, $P < 0.05$; 116.30 vs. 150.39 μg/dL, $P < 0.001$; 8.57 vs. 16.16 μg/dL, $P < 0.001$; 1.92 vs. 2.31 mg/dL, $P < 0.05$, respectively). Multivariate analysis showed that there was a significant trend between levels of zinc, copper, selenium, and magnesium and the prevalence of T2DM. **Conclusions:** The levels of selenium, zinc, copper, and magnesium were significantly lower in patients with T2DM when compared to healthy counterparts.

Keywords: Cardiovascular disease, HbA1c, neuropathy, selenium, zinc

Introduction

Diabetes is one of the most common metabolic disorders in the world and the rate of diabetes has reached the proportions of a global pandemic. In this regard, India is an epicentre of diabetes with home to 77 million people with Diabetes Mellitus (DM).[1] Patients with Type 2 Diabetes Mellitus (T2DM) are at higher risk of developing insulin resistance, obesity, and prevalence of cardiovascular disorders later in their lives.[2]

Some studies have suggested that several trace elements have multiple roles in body metabolism, chronic hyperglycemia, and cellular homeostasis.[3-5] In addition, the early imbalances of trace elements in T2DM cause increased oxidative stress that may contribute to the development of T2DM and which would exacerbate the risk of diabetic complications.[6]

Numerous studies have evaluated the association between trace elements and T2DM. Magnesium, chromium, zinc, and selenium supplementation has been shown to improve insulin sensitivity.[4]

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Insulin action of reducing blood glucose has been found to be enhanced by trace elements such as chromium, magnesium, vanadium, zinc, manganese, molybdenum, and selenium.[5] Zinc plays an important role in glucose metabolism, the formation of insulin crystals, release, and transport of insulin. Zinc supplementation in patients with T2DM significantly reduces serum levels of cholesterol and glycated haemoglobin (HbA1c) in the blood thereby improving the symptoms of diabetes.[7] Copper together with zinc, produces balanced oxidant-antioxidant mechanisms.[8] Magnesium supplementation improved insulin sensitivity and beta cell of the pancreas and therefore magnesium supplements lower the risk of T2DM. Chromium acts as a blood sugar modulator that could guard against high blood sugar level.[9] Selenium is an essential trace element that helps in protecting tissues and membranes from oxidative stress. It has also shown to have insulin-like actions in both *in vivo* and *in vitro*.[10]

The HbA1c is a glycated form of haemoglobin. It is formed by non-enzymatic conversion of glucose to haemoglobin. Increasing levels of HbA1c in diabetic patients is due to increase in blood glucose concentrations.[11] Some reporters have alluded that glycated proteins binding to transition metals such as copper and iron may result in glycocholates formation.[11,12]

Present study aimed to summarize the difference in zinc, copper, chromium, selenium, and magnesium levels between type 2 diabetic and non-diabetic healthy individuals. A secondary goal of this research is to estimate their association with the duration of diabetes, exercise, habituation, lifestyle or socioeconomic status and chronic complications of diabetes.

Material and Methods

Subject

This cross-sectional study was carried out in a tertiary center in XXXXXXXX (*name of the country is masked for blinded review*). The study comprised of confirmed cases of T2DM patients and attending a diabetic clinic and irrespective of sex, religion, and socio-economic status. The following participants were excluded from this study: Pregnant or lactating women and diabetic patients with known malignancy. The study protocol was approved by the Independent Ethics Committee and the study procedure was in accordance with the principles of the Declaration of Helsinki.

Sample size was calculated by:

Equation:

$$n = \frac{Z^2\ P(1-P)}{d^2}$$

n = Sample Size = 122

Z = Z Statistic for a level of confidence = 1.96

P = Expected prevalence or proportion = 8.7%

d = Precision = 5%

Level of confidence = 95%

Disease prevalence in India = 8.7%

Biochemical analysis

Blood samples (3-5 ml) were collected, centrifuged for 10 mins at 4000 rpm at 4°C and serum was separated and stored at -80°C till further analysis. A socio-demographic profile such as age, sex, Body Mass Index (BMI), smoking habit, alcohol consumption, sedentary lifestyle, duration of diabetes in patients with DM. A standard glucometer was used to measure blood glucose for all participants. Estimations of haemoglobin, total leucocyte count, red blood cell count, blood glucose, bilirubin, uric acid, platelet count, total protein, serum creatinine and urea, and liver function test were performed.

Elemental analysis

The concentrations of the trace elements such as zinc, copper, chromium, selenium, and magnesium were determined by the Inductively Coupled Plasma Optical Emission Spectrometer (ICP-OES). Samples were diluted 5-fold and 25-fold using an acid matrix-matched blank solution and analysed at the wavelengths with atomic absorption spectrophotometer. The concentration of each element was determined by measuring the intensities at wavelength in colorimetry. The concentration of applied elements and various parts of the equipment were verified by blank samples.

Statistical analysis

The data was entered in MS Excel spreadsheet, and analysis was done using an advanced statistical tool of Microsoft Excel 2010. Qualitative data was presented as number and percentages, while quantitative data was presented as mean (standard deviation [SD]). Normal distribution of quantitative data was assessed by Shapiro-Wilk test. Comparison of qualitative variables between the groups was done using Mann-Whitney U test. Quantitative variables were compared using independent t-test (for normal distribution), z-test (when the distribution is not normal) and Mann Whitney test (for non-parametric data) between two groups. For quantifying association, odds ratio with 95% confidence interval was used and significance of odds ratio was calculated by Fisher's-Exact Probability statistic. A $P < 0.05$ was considered statistically significant. The work was approved by the ethics committee of this university and the approved date was 21.05.2019.

Results

Total of 200 patients were included in this study including 150 with T2DM and 50 control cases. The mean (SD) age was 52.5 (9.69) years with majority of the cases (63.3%) and controls (52%) were in the age group of 51 to 65 years. A male preponderance was found with a men-to-women ratio of 2:1. There was no significant difference in BMI in both the groups (24.2 vs. 23.9 kg/m^2). Biochemical parameters are summarized in Table 1. The mean HbA1c levels were statistically significant between diabetic patients and the healthy control group (9.83 vs. 5.46; $P < 0.001$). Considering the duration of diabetes, 37.33% had diabetes for 5 years while 62.66% for ≥5 years. Among diabetic patients, nearly half of the patients (52.0%) had lack of regular exercise and 66.0% of patients were leading a sedentary lifestyle. Half of the patients were habituated to either alcohol, smoking, or tobacco chewing. 62.6% belonged to the middle-class. Oral Antidiabetic Drugs (OADD) were the most commonly prescribed drug (81.3%) followed by a combination of OADD and insulin (10.7%), and insulin alone (4.7%). Hypertension (42.0%) was the most commonly associated comorbidities among patients with T2DM followed by Hypothyroidism (14.0%). Total 57.3% (n = 86) of diabetic patients had uncontrolled blood sugar with HbA1c >9 and only 14.6% (n = 22) had good control of blood sugar with HbA1c <7. Majority (45.3%) of diabetic patients had diabetic peripheral neuropathy while 36.7%, 20.7%, 17.3%, 8.7%, and 6% had diabetic retinopathy, coronary artery disease, diabetic nephropathy, peripheral vascular disease, and cerebrovascular accident respectively.

The level of essential trace elements in diabetic patients and healthy control are illustrated in Table 2. The average level of zinc, copper, selenium, and magnesium was significantly lower in patients with diabetes as compared to the healthy control group (62.89 vs, 74.95 μg/dL, $P < 0.05$; 116.30 vs. 150.39 μg/dL, $P < 0.001$; 8.57 vs. 16.16 μg/dL, $P < 0.001$; 1.92 vs. 2.31 mg/dL, $P < 0.05$, respectively). The mean level of chromium was comparatively lower in diabetic patients when compared to the healthy control group.

The mean level of HbA1c was significantly associated with selenium (r = -0.2, $P < 0.05$) but not with other trace elements. Among trace elements, Selenium was significantly associated with copper (r = 0.4, $P < 0.05$) while correlation of zinc with magnesium was significant (r = 0.3, $P < 0.05$).

Multivariate analysis of trace elements in diabetic patients and the healthy control group have shown that zinc, copper, chromium and selenium were found to be significantly associated with prevalence of T2DM ($P < 0.05$) Table 3. However, there was no significant difference between trace elements and patient's duration of diabetes, exercise, habituation, life style or socioeconomic status was observed. Similarly, no such significant findings were observed in patient with the various complications of diabetes.

Discussion

Apart from macronutrients, micronutrients like trace elements are also being evaluated for cause or association with development and progression of diabetes and the major attributable comorbidities with it includes hypertension.[13,14]

A cross sectional study have suggested a possible relationship between zinc deficiency and hypertension.[13] Potassium supplementation reduced the risk of salt-induced blood pressure, hypertension, dyslipidaemia, and obesity.[15-17] In addition, Shaaban *et al.*[18] have reported an association between high iron stores and increased risk of cardiovascular disease.

Table 1: Biochemical parameters of type 2 diabetic patients and healthy controls

Parameters	Test group (n=150) Mean (SD)	Control group (n=50) Mean (SD)	P
Hemoglobin (g/dL)	10.95 (2.39)	11.45 (2.05)	0.160
TLC (cells/mm^3)	9500.70 (5469.51)	9473.00 (4711.11)	0.970
PC (million cells/μL)	1.94 (0.78)	2.09 (0.79)	0.260
RBC (million cells/μL)	4.24 (3.25)	4.65 (0.68)	0.850
Sodium (mM/L)	138.74 (6.36)	136.98 (8.87)	0.120
Potassium (mM/L)	5.09 (5.35)	4.24 (0.91)	0.260
Serum urea (mg/dL)	73.85 (59.48)	35.02 (12.86)	<0.001
Serum creatinine (mg/dL)	2.51 (2.25)	0.92 (0.36)	<0.001
FPG (mg/dL)	171.02 (62.52)	99.52 (10.57)	<0.001
Uric acid (mg/dL)	6.61 (2.37)	5.46 (0.49)	0.001
Total bilirubin (mg/dL)	0.62 (0.47)	0.56 (0.32)	0.386
SGOT (IU/L)	69.26 (71.11)	28.56 (13.45)	0.095
SGPT (IU/L)	80.28 (63.66)	33.96 (16.60)	0.047
ALP (IU/L)	417.99 (1263.24)	231.38 (121.22)	0.299
Total protein (g/dL)	6.68 (0.99)	6.74 (0.99)	0.688
Albumin (g/dL)	3.79 (0.66)	3.86 (0.67)	0.573
Cholesterol (mg/dL)	173.59 (57.01)	162.9 (50.89)	0.240
Triglyceride (mg/dL)	172.94 (65.74)	152.42 (58.75)	0.064
HDL (mg/dL)	32.47 (23.31)	42.7 (14.03)	0.006
LDL (mg/dL)	72.86 (30.53)	61.84 (27.92)	0.025

Data shown as mean (SD). ALP, alkaline phosphatase level; FPG, fasting blood glucose; RBC, Red blood cell count; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; TLC, total leucocyte count; HDL, High density lipoprotein; LDL, Low density lipoprotein

Table 2: The level of essential trace elements in type 2 diabetes mellitus patients and healthy controls

Parameters	Normal range	Test group (*n*=150)	Control group (*n*=50)	*P*
Zinc	75-120 μg/dL	62.89 (30.67)	74.95 (18.11)	0.009
Copper	70-140 μg/dL	116.30 (51.79)	150.39 (47.39)	<0.001
Chromium	<13 μg/dL	7.00 (3.30)	6.00 (5.50)	0.833
Selenium	6-17 μg/dL	8.57 (8.30)	16.16 (5.70)	<0.001
Magnesium	1.8-3.6 mg/dL	1.92 (0.63)	2.31 (1.35)	0.046

Data shown as mean (SD)

Table 3: Multivariate analysis of trace elements in cases vs. Controls

Parameters	Odds ratio	95% CI		*P*
		Lower	Upper	
Zinc	1.028	1.013	1.043	<0.001
Copper	1.008	1.000	1.016	0.04
Selenium	1.028	1.015	1.042	<0.001
Magnesium	0.093	0.017	0.516	0.007

A previous study from India showed that the serum level iron was higher in the patients with poorly controlled T2DM.[14]

The present study could not draw the association between comorbidity associated with a deficiency of trace elements. It has been reported that magnesium deficiency is associated with complications such as retinopathy, thrombosis, and hypertension.[14] Cross-sectional study showed that a serum zinc deficiency is associated with retinopathy in T2DM.[19] Similarly, in the present study majority of diabetic patients had microvascular complications such as peripheral neuropathy, diabetic retinopathy, coronary artery disease, diabetic nephropathy, peripheral vascular disease, and cerebrovascular accident. Low levels of chromium and magnesium were significantly associated with diabetic retinopathy and diabetic nephropathy. Comparative case control study (n = 50) evaluated that serum copper levels were significantly increased in cases of retinopathy than healthy controls (238.1 vs. 106.4 μg/dL) suggesting that high levels of copper enhance the metal-dependent free radical reaction. The serum zinc level was lower in cases of retinopathy than control cases (50.5 vs. 90.16 μg/dL).[20]

Atalay *et al.*[21] found that the serum copper, zinc, iron, and magnesium levels were significantly lower in patients with T2DM compared with the healthy controls ($P < 0.05$). Among the previous literature Hussain *et al.*[22] confirm the efficiency of trace elements in the development of DM. Furthermore, serum magnesium and zinc levels were found to be significantly lower in patients with T2DM than healthy control. However, serum copper levels were found to be comparatively higher in patients with T2DM. In parallel to these studies, the present study revealed significantly lower mean levels of zinc, copper, selenium, and magnesium in patients with T2DM than the healthy control groups. Whereas the mean chromium level was comparatively lower in cases when compared to controls. Recently published noteworthy study revealed that mean zinc levels were significantly lower in patients with T2DM than healthy individuals ($P < 0.01$), whereas copper and ferritin levels were significantly higher in diabetic cases when compared to healthy control.[23] Similarly, Hasanato also reported corroborating findings indicating altered levels of serum Cu, Zn and Se in patients with T2DM than normal healthy counterparts.[24]

In this study, HbA1c levels were inversely correlated with selenium in T2DM groups. Similarly, a previous prospective cohort study demonstrated a negative correlation of zinc, magnesium, and selenium with HbA1c levels in patients with T2DM.[25] In addition, Devi *et al.*[26] reported that HbA1c levels were negative correlated with serum selenium level in the patients with T2DM (r = -0.232, $P < 0.001$). In contrast, Sobczak *et al.*[27] showed a significant correlation between selenium level and HbA1c. HbA1c levels were positively correlated with copper, magnesium, and copper to zinc ratio was inversely correlated with HbA1c in the T2DM group. The negative correlation between selenium and HbA1c levels was associated with poor control of the disease which can lead to oxidative injury.[28] Therefore, supplementation of these elements might be beneficial both for controlling diabetes and preventing long term diabetic complications.

There was a significant trend between levels of zinc, copper, selenium, and magnesium and the prevalence of T2DM. This is in line with the population-based Nord-Trøndelag Health Study (The HUNT Study) evaluated an increasing prevalence of diabetes with significant increase in odds ratio (95% CI) bromine ($r = 0.52$, $P = 0.0032$), chromium ($r = 2.78$, $P = 0.001$), iron ($r = 2.97$, $P = 0.009$), nickel ($r = 2.24$, $P = 0.016$), silver ($r = 2.78$, $P = 0.006$), zinc ($r = 2.19$, $P = 0.038$), and cadmium ($r = 1.99$, $P = 0.027$).[29] Recently published metanalysis revealed that cadmium significantly increased tendency for insulin resistance thus increasing the chances of developing T2DM.[30] A significant reduction was noted in serum sodium in patients with T2DM. The study also reported non-significant association was observed between serum potassium and the incidence of T2DM.[31] Moreover, Palathingal *et al.*[32] demonstrated a negative correlation between serum magnesium and HbA1c.

Overall, this study validates that trace element deficiencies appear to be an additional risk factor in the development and prognosis of T2DM and they also contribute to the pathogenesis of diabetic complications. Their repletion in early stage might be helpful for primary care physician for an effective therapeutic intervention and in prevention of the progression of the T2DM and its complications, along with a glycaemic control.

Limitations

The limitation of this study is its cross-sectional design, as without a cohort study, precise evaluation of role of trace elements in diabetic nephropathy is difficult.

Conclusions

The levels of selenium, zinc, copper, and magnesium were significantly lower in patients with T2DM when compared to healthy counterparts. The study has demonstrated that a significant decrease in micronutrients may influence the progression of T2DM. Taken together, the results of this study suggested that there is need to monitor trace element levels in diabetic patients. Early evaluation of trace element deficiencies will enable the primary care physician to understand the etiopathogenesis in order to provide effective treatment modalities. Further clinical studies are required to recognize the role of trace elements in the development of diabetes.

Key points

- The serum contents of zinc, copper, selenium, magnesium, and chromium were lower in diabetic patients than in non-diabetic controls.
- Elevated HbA1c was significantly associated with decreased selenium levels.
- Lower concentrations of zinc, copper, chromium and selenium were found to be significantly associated with an increased incidence of T2DM.

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Conflicts of interest

There are no conflicts of interest.

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