

Serum trace elements in insulin-dependent and non-insulin-dependent diabetes: a comparative study

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Background: Diabetes mellitus is associated with imbalance in body trace elements. The aim of the current investigation was to compare the levels of trace elements (Zn, Mg, Mn, Cu, Na, K, Fe, Ca, Cr, and Se) in insulin dependent (IDDM) and non-insulin dependent (NIDDM) diabetes.

Methods: A total of 100 patients with diabetes (40 IDDM and 60 NIDDM) and 50 healthy subjects were recruited in the study from both genders. Biochemical measures include glucose, lipids, and HbA1C.

Results: The results showed that Zn, Mg, Cu and Cr were significant lower in patients with diabetes compared to the control group ($P < 0.01$). In addition, Zn and Cr were significantly lower in IDDM than NIDDM ($P < 0.05$). Moreover, Zn and Mg levels were inversely correlated with HbA1c in IDDM and NIDDM ($P < 0.05$). Zn was inversely correlated with fasting blood glucose in IDDM ($P < 0.05$). Finally, no correlation between trace element levels with BMI was found ($P > 0.05$).

Conclusion: Disturbance in trace element profile among IDDM and NIDDM is similar.

Keywords: trace elements, diabetes mellitus, IDDM, NIDDM

Introduction

Diabetes mellitus is a common metabolic disease that is characterized by misregulation of blood glucose levels leading to hyperglycemia.^{1,2} The disease affects millions of people worldwide and the number of people affected by diabetes is increasing.³

The prevalence of diabetes is high among Middle Eastern and North African countries with frequencies between 4% and 10%.^{4,5} Diabetes is associated with several complications that include renal deteriorations, retinopathy leading to vision disturbance, nerve damage and predisposition to cardiovascular diseases.^{6,7} Diabetes can be divided into insulin-dependent (IDDM) and non-insulin-dependent diabetes (NIDDM).⁸ In the NIDDM, hyperglycemia arises from the loss of normal tissue sensitivity to insulin (also known as insulin resistance).⁹ In IDDM, hyperglycemia arises from insufficient production of insulin from pancreatic cells due to autoimmunity.¹⁰ The two types differ also in the management of the disease and its complications.^{11,12}

Previous studies have shown alterations in the balance of trace elements in patients with diabetes.^{13,14} Trace elements play important roles in body metabolism and cellular homeostasis.¹⁵ This includes production, secretion and insulin activity pathway.¹⁶⁻¹⁸ For example, insulin mechanism of action has been shown to be modulated by Mg, Cr, Zn, Mn, Se and others.¹⁶⁻¹⁸ Since IDDM and NIDDM differ in their etiology and management, we hypothesized that the balance of trace elements might differ between the two types. In support of this hypothesis, a previous study from Sudan showed significant

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difference in the levels of Cr between IDDM and NIDDM.¹⁹ Therefore, in the current study, impairment of trace elements among IDDM and NIDDM patients was examined. In addition, levels of trace elements in the two groups were correlated with glycemic control and lipid profile parameters.

Methods

Participants

A hundred patients with diabetes (40 IDDM and 60 NIDDM) (61 male, 39 female) were recruited from Jabir Abu Aliz Diabetes Center (Khartoum, Sudan). For comparison, 50 healthy subjects (30 male and 20 females) were included as controls. Inclusion criteria for diabetes group were: HbA1C above 6.5%, random blood glucose ≥ 11 mmol/L, fasting blood glucose (FBG) ≥ 7.7 mmol/L. The threshold of FBG was selected slightly above guidelines for defining diabetes (ie, 7 mmol/L) to exclude borderline patients. Exclusion criteria include patients with renal complications or failure, acute kidney infection, chronic illness other than diabetes that include liver disease, anemia, and thyroid disease, and vitamin/mineral supplements.^{19–21} The study was approved by Khartoum State Ministry of Health Research Ethics Committee, Khartoum, Sudan and by Research Ethics Committee of Applied Medical Sciences at Taibah University, Madinah, Saudi Arabia. Both committees utilized the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was taken from participants after a full description of study objectives and procedures.

Anthropometric parameters

Body mass index (BMI) and waist circumference were measured as previously described.²² Classifications of BMI were:

normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), and obese (≥ 30.0 kg/m²).

Biochemical parameters

Fasting blood samples (about 3 mL each) were collected from participants in plain tubes using disposable syringes. All blood samples were allowed to clot at room temperature for 30 minutes and then centrifuged at 4,000×g to obtain the serum. Total cholesterol, triglyceride, HDL, and LDL were measured using a Hitachi autoanalyzer 704 (Hoffman-La Roche Ltd., Basel, Switzerland). Trace elements (Zn, Mg, Mn, Cu, Fe, Ca, Cr and Se) were determined using WFX-320 Atomic Absorption Spectrophotometer (Beijing Rayleigh Analytical Instrument Corporation (BRAIC), Beijing, China).²³ Na and K were determined using a flame photometer (JENWAY, model PFP7, Stone, UK).²⁴

Statistical analysis

The data were analyzed using SPSS version 19 (IBM Corporation, Armonk, NY, USA). Comparisons that include three groups or more were conducted using ANOVA followed by Tukey post hoc test. Student's *t*-test and Pearson correlation were used for data that involved two groups. *F* comparisons that involve frequencies were performed using chi-squared/Fisher's exact test. A *P*<0.05 was used to indicate significant differences.

Results

Table 1 shows demographics of participants. The mean age of IDDM, NIDDM and controls was 45±1.7, 46±3.6 and 45±2.4, respectively (*P*>0.05). In addition, gender ratios were not different between the three groups (Table 1, *P*>0.05). With respect to BMI and waist circumference, they were slightly higher in NIDDM than other groups (*P*<0.05). In addition,

Table 1 Demographics of participants

Characteristics	IDDM n=40	NIDDM n=60	Control n=50	P-value
Age, years	45±1.7	46±3.6	45±2.4	0.11 ^a
Gender (male, female)	(27, 13)	(34, 26)	(30, 20)	
BMI, kg/cm ²	23±3.3	27±4.7*	23±2.4	<0.001 ^a
Normal, 18.5–24.9 (%)	37 (92.5)	20 (33.3)	43 (86)	
Overweight, 25–29.5 (%)	3 (7.5)	33 (55.0)	7 (14)	<0.001 ^b
Obese, >30 (%)	0 (0)	7 (11.7)	0 (0)	
Waist circumference, cm	80.6±24.9	86.1±24.2	81.1±22.4	0.42 ^a
≤90 (%)	38 (95)	22 (36.7)	45 (90)	
>90 (%)	2 (5)	38 (63.3)	5 (10)	<0.01 ^b
Period of diabetes, years	23.5±7.1*	5.8±1.8	–	<0.001 ^c

Notes: **P*<0.001. ^aANOVA *P*-value; ^bFisher's exact *P*-value; ^c*t*-test value.

Abbreviations: BMI, body mass index; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

the frequency of obese patients and those with a waist circumference above 90 cm was higher in NIDDM compared to other groups ($P<0.01$, Table 1).

Table 2 shows biochemical parameters between different groups. FBG, HbA1c, total cholesterol, triglyceride, LDL and HDL were significantly higher in patients with diabetes (IDDM and NIDDM) compared to the control group ($P<0.05$) and the majority are within normal ranges (as shown by frequency data, Table 2) suggesting that the patients included in this study have a relatively good lifestyle and dietary habits.

With respect to trace elements, Zn, Mg, Cu and Cr were significantly lower in patients with diabetes compared to the

control group ($P<0.05$, Table 3). In addition, Zn and Cr were significantly lower in IDDM than NIDDM ($P<0.05$).

The level of serum trace elements was compared in patients with diabetes according to different demographic and clinical parameters. When gender was considered Zn levels were higher in females compared to males ($P<0.05$), whereas Fe and Ca were significantly higher in males compared to females ($P<0.01$). Sodium was higher in normotensive compared to hypertensive patients ($P<0.01$). However, no significant differences were detected with respect to trace elements among patients with diabetes when BMI was considered ($P>0.05$).

Table 2 Fasting glucose, glycemic control and lipid profiles of participants

Parameters	IDDM n=40	NIDDM n=60	Control n=50	P-value
FBG, mmol/L	9.1±2.6*	8.8±1.7*	4.7±1.3	>0.001 ^a
HbA1c %	8.3±3.1*	8.1±3.7*	5.1±1.1	>0.001 ^a
≤6%, n (%)	18 (45)	31 (51.7)	50 (100)	0.42 ^b
>6%, n (%)	22 (55)	29 (48.3)	0 (0)	
Total cholesterol (mmol/L)	4.3±1.1*	4.1±2.3*	3.2±0.7	0.002 ^a
≤6.2 mmol/L, n (%)	27 (67.5)	45 (75)	48 (96)	0.0016 ^b
>6.2 mmol/L, n (%)	13 (32.5)	15 (25)	2 (4)	
Triglyceride (mmol/L)	1.5±0.4*	1.6±0.6*	1.0±0.3	>0.001 ^a
≤2.2 mmol/L, n (%)	29 (72.5)	47 (78.3)	49 (98)	0.002 ^b
>2.2 mmol/L, n (%)	11 (27.5)	13 (21.7)	1 (2)	
LDL (mmol/L)	2.9±0.4*	3.1±0.7*	1.8±0.2	>0.001 ^a
≤4.1 mmol/L, n (%)	26 (65)	38 (63.3)	47 (94)	0.0004 ^b
>4.1 mmol/L, n (%)	14 (35)	22 (36.7)	3 (6)	
HDL (mmol/L)	1.5±0.5*	1.5±0.2*	2.6±0.2	>0.001 ^a
>1.0 mmol/L, n (%)	29 (72.5)	41 (68.3)	45 (90)	0.02 ^b
≤1.0 mmol/L, n (%)	11 (27.5)	19 (31.7)	5 (10)	

Notes: * $P<0.05$. ^aANOVA P-value; ^bFisher's exact/chi-squared test P-value.

Abbreviations: FBG, fasting blood glucose; IDDM, insulin-dependent diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIDDM, non-insulin-dependent diabetes mellitus.

Table 3 Levels of serum trace elements

Characteristics	IDDM n=40	NIDDM n=60	Control n=50
Zinc (Zn), µmol/L	10±1.8*	12±1.7 ^a	16.1±2.3
Magnesium (Mg), mmol/L	0.72±0.2 ^a	0.72±0.4 ^a	0.91±0.2
Manganese (Mn), µg/L	0.25±0.2	0.25±0.2	0.26±0.1
Copper (Cu), µg/dL	140.7±16.7 ^a	141.1±21.3 ^a	152.3±17.4
Sodium (Na), mmol/L	141.3±22.5	139.4±16.9	140.1±18.4
Potassium (K), mmol/L	3.4±2.5	3.9±1.2	4.1±0.6
Iron (Fe), µmol/L	22.6±6.4	23.3±6.1	24.6±5.8
Calcium (Ca), mmol/L	2.31±0.4	2.36±0.2	2.4±0.5
Chromium (Cr), µg/L	1.4±1.1*	1.9±1.2 ^a	2.5±0.9
Selenium (Se), µg/L	134±13.5	134±14.6	138±10.4

Note: * $P<0.01$; ^a $P<0.05$.

Abbreviations: IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

Table 4 shows correlations between the serum levels of trace elements and BMI, FBG, and HbA1c of the IDDM, NIDDM and control subjects. Zn and Mg levels were inversely correlated with HbA1c in IDDM and NIDDM ($P<0.05$). Zn was inversely correlated with FBG in IDDM ($P<0.05$).

Discussion

In the current study, modulation of trace elements (Zn, Mg, Mn, Cu, Na, K, Fe, Ca, Cr and Se) among IDDM and NIDDM patients was examined. The serum Zn, Mg and Cu were found to be lower patients with diabetes than healthy controls.

Magnesium is an essential ion for all organisms and it is present in every cell in the human body.²⁵ The role of Mg in glucose metabolism, transport and homeostasis is well documented.^{26,27} Several enzymes that involved in glucose metabolism require Mg ions for their activity.²⁸ In addition, insulin has been shown to affect cellular Mg uptake.²⁹ Alternatively, Mg plays a role in the release of insulin from pancreatic cells.^{30,31} Magnesium could also affect glucose homeostasis in an insulin independent pathway via modulation of membrane bound sodium, potassium ATPase activity, which is involved in cellular glucose transport.^{32,33} The results of the current investigation showed low levels of Mg in patients with diabetes, which was detected in both IDDM and NIDDM. In addition, Mg levels were negatively correlated with HbA1c in both diabetic subgroups. This highlights the importance of glycemic controls in maintaining ion balance inside the body. Disturbance of Mg levels in patients with diabetes agrees with previous reports that were conducted in other countries.^{16,34–36} Factors that might contribute to the low levels of Mg (also

known as hypomagnesaemia) in diabetes include impairment of tubular reabsorption of Mg by the action of glycosuria and hyperglycemia.³⁷ In addition, disturbance in insulin levels affects cellular Mg uptake.^{30,31} Since Mg is impaired in both IDDM and NIDDM and Mg levels were negatively correlated with HbA1c, hyperglycemia seems to be the major factor that affects Mg levels in patients with diabetes.

Zinc is important for glucose homeostasis as it is involved the synthesis, storage and secretion of insulin, being a component of several metabolic enzymes, regulation of immunity and suppression of inflammation.³⁸ Zinc also is important in normalization of the oxidative stress that plays a role in the β cell destruction.³⁹ Abnormal zinc metabolism is suggested to play a role in the etiology of diabetes and some of its complications.⁴⁰ In the present study, serum zinc levels were found to be significantly lower in patients with diabetes, which was consistent with previous findings.^{41,42} Similar to Mg, Zn was impaired in both IDDM and NIDDM. In addition, Zn levels were correlated with HbA1c. In a previous study, Zn was found to be deficient in the serum, leukocyte and hemoglobin of the IDDM subjects but not in NIDDM.⁴³ In another study, plasma zinc was lower in both IDDM and NIDDM compared to healthy controls.⁴⁴ Conversely, Zn was reported to be elevated in erythrocytes of children with IDDM.⁴⁵ Thus, hyperglycemia seems to play a major role in the determination of Zn levels in patients with diabetes.⁴⁶

Copper is an essential element that is important for energy production as it is a component of the mitochondrial cytochrome oxidative phosphorylation system.⁴⁷ Therefore, Cu deficiency is expected to cause distortion of mitochondria, particularly in metabolically active cells as pancreatic and

Table 4 Correlations between the serum levels of trace elements and (BMI, FBG and HbA1c) of both diabetic groups and control healthy subjects

Elements	IDDM			NIDDM			Control		
	BMI kg/cm ²	FBG mmol/L	HbA1c %	BMI kg/cm ²	FBG mmol/L	HbA1c %	BMI kg/cm ²	FBG mmol/L	HbA1c %
Zn	-0.160	-0.41*	-0.36*	-0.08	-0.22	-0.39*	-0.12	-0.03	-0.01
Mg	-0.17	-0.19	-0.30*	-0.03	-0.08	-0.29*	-0.04	-0.01	-0.01
Mn	-0.08	-0.08	-0.01	-0.07	-0.11	-0.02	-0.01	0.01	0.02
Cu	-0.02	0.09	0.02	-0.05	-0.07	-0.11	-0.01	0.02	0.03
Na	-0.01	0.04	0.03	-0.01	0.06	-0.04	-0.02	0.03	0.07
K	0.03	0.03	0.08	0.03	0.04	0.09	0.04	0.02	0.02
Fe	0.01	0.02	0.04	0.01	0.01	0.02	0.01	0.06	0.03
Ca	-0.01	0.03	0.03	-0.02	0.02	0.03	-0.05	0.05	0.02
Cr	-0.06	0.18	-0.03	-0.17	0.03	-0.02	-0.01	0.01	0.04
Se	0.03	0.01	0.03	0.05	0.04	0.02	-0.12	0.02	0.06

Note: * $P<0.05$.

Abbreviations: BMI, body mass index; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

liver cells.⁴⁸ In the current study, Cu levels were found to be slightly decreased in IDDM and NIDDM patients with comparable magnitudes. Previous studies have reported conflicting results with respect to Cu levels in diabetes patients.⁴⁹ For example, increase in plasma Cu levels was reported in studies from Taiwan, Brazil and Egypt^{47,50,51} whereas decrease or no change in Cu levels was reported in studies from the USA,⁵² Germany,⁵³ Austria⁵⁴ and Sudan (current study). The discrepancy could be due to differences in lifestyles and dietary habits between different populations.

The results found decreases in Cr levels in both IDDM and NIDDM patients. This is in agreement with most previous studies.^{16,55,56} Cr is involved in insulin action and its chromium deficiency is related to glucose intolerance and insulin resistance in patients with diabetes.⁵⁷ In addition, some studies have reported a lower risk of NIDDM in adults who were taking chromium-containing supplements.⁵⁷ The results showed lower levels of Cr in IDDM than NIDDM. This suggests that insulin might play a role in Cr balance inside the body. However, one previous study from Germany has shown increases in Cr in plasma and polymorphonuclear cells of NIDDM.⁴⁵ More studies are required to investigate the differences in Cr levels among different diabetic groups and in different populations.

Limitations

Among the study limitations is that some factors that might impact trace elements such as vitamin D levels, occupation and diabetes management medications were not evaluated in the sample. Taking into consideration such factors in future studies is recommended. In addition, the current findings need to be confirmed in a larger study from Sudan as the current sample size is relatively small. Moreover, evaluation of the status of trace elements in subjects with prediabetes and comparing that to diabetic groups is recommended in future investigations.

Conclusion

In Sudanese patients with diabetes, the metabolism of several trace elements was altered, namely, Zn, Mg, Cu, and Cr. The major finding was a decrease in the levels of Zn, Mg, Cu and Cr. Zn and Mg were inversely correlated with HbA1c in all patients with diabetes. Zn was inversely correlated with FBG in NIDDM patients.

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Disclosure

The authors report no conflicts of interest in this work.

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