

Trace elements in type 2 diabetes mellitus and their association with glycemic control

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Abstract:

Background: Alterations in serum levels of trace elements reported in type 2 diabetes mellitus (T2DM) have been linked with induction of T2DM and associated complications.

Objectives: To assess serum levels of copper (Cu), zinc (Zn) and selenium (Se) in T2DM patients with adequate and poor glycemic control.

Patients and methods: This study was performed at King Khalid University Hospital, Riyadh. A total of 100 consenting T2DM patients comprising of 50 patients with glycated hemoglobin (HbA1c) less than 6.5% and 50 patients with HbA1c more than 6.5% along with a group of 50 normal healthy individuals were included in the study. Serum levels of Cu, Zn and Se were measured by inductively coupled plasma-mass spectrometry (ICP-MS) instrument.

Results: Among T2DM patients with HbA1c <6.5%, mean serum Cu levels (13.4+4.3 μ mol/L) were not different from the controls (14.5+1.92 μ mol/L) whereas Zn (9.9+2.7 μ mol/L vs 15+3.2 μ mol/L; p<0.0001) and Se levels (1+0.2 μ mol/L vs 1.62+0.2 μ mol/L; p<0.0004) were lower than the controls. Among T2DM patients with HbA1c >6.5% mean serum Cu (18.1+4.1 μ mol/L vs 14.5+1.9 μ mol/L; p<0.0001), Zn (15+3.2 μ mol/L vs 13.5+1.9 μ mol/L; p<0.009) and Se (1.62+0.2 μ mol/L vs 1.17+0.16 μ mol/L; p<0.0001) were significantly higher than the controls. HbA1c% negatively correlated with HbA1c >6.5% (r = -0.302; p<0.03).

Conclusion: Cu, Zn and Se homeostasis was altered in T2DM patients and varied with glycemic control.

Keywords: Copper, Zinc, Selenium, trace elements, diabetes mellitus.

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Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by impaired insulin secretion and altered glucose metabolism resulting in hyperglycemia.¹ Trace elements including zinc (Zn), copper (Cu) and selenium (Se) are involved in several physiological functions at cellular level² including functions related to insulin and glucose metabolism.³ Altered body composition of these micro-nutrients have been implicated in the development of T2DM.⁴ Hyperglycemia in diabetes on the other hand

has been blamed for alterations in serum levels of these trace elements⁵ resulting in enhancement of oxidative stress and decreased production of insulin.⁶

Zn as an anti-oxidant trace element not only potentiates the actions of insulin⁷ but is also crucial for the production of insulin.⁸ Zn deficiency reported in T2DM is believed to be due to increased urinary losses of this trace element and the reduced Zn status exhibits a negative correlation with hyperglycemia and poor glycemic control.⁹ Elevated levels of Cu¹⁰ a pro-oxidant trace element, are not only implicated in increased oxidative stress in T2DM but also contribute to insulin resistance and hyperglycemia.¹¹ Despite these observations data regarding serum levels of Zn and Cu in T2DM are inconsistent with claims that Zn and Cu concentrations are not altered in T2DM.¹² Moreover, Zn supplementation has been shown to exhibit a negative correlation of with glycated hemoglobin (HbA1c).¹³ Similarly, Se is considered as an anti-oxidant trace element and higher Se concentrations have been associated with

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decrease prevalence of T2DM.¹⁴ On the contrary there is evidence that higher serum Se concentration is associated with higher prevalence of T2DM, higher fasting plasma glucose and HbA1c percentage in T2DM.¹⁵

In the backdrop of conflicting data for trace elements in T2DM, this study was performed to assess the levels of Zn, Cu and Se among patients with T2DM and to investigate whether the levels of trace elements in T2DM are associated with glycemic control.

Patients and methods

This study was performed in the Clinical Chemistry Unit at King Khalid University Hospital, Riyadh between June 2015 and September 2016. A total of 100 consenting patients both males and females with T2DM and 50 normal healthy controls were included in the study. T2DM patients were grouped on the basis of HbA1c >6.5% (50 patients) and HbA1c <6.5% (50 patients) into two groups with poor and optimal glycemic control respectively. Apart from the demographic details data regarding the duration of illness, current treatment for T2DM, vitamin and mineral intake and smoking status were also recorded. Inclusion criteria for patients were confirmed diagnosis of T2DM with positive glucose tolerance test, absence of coexisting acute or chronic illnesses other than T2DM associated complications and not receiving vitamin or mineral supplements at the time of inclusion in the study or at least three months before. Inclusion criteria for normal controls were absence of any acute or chronic illness and it was ensured that none of the controls was receiving oral supplements of vitamins or minerals at the time of collection of blood sample or at least three months before.

Table describes the characteristic features of the patients and controls. In the HbA1c < 6.5% group there were 31 females and 19 males with the mean age of 55.4 + 6.7 years whereas in the HbA1c > 6.5% group comprised of 33 females and 17 males with the mean age of 57.8 + 14.3 years. The control group had 28 females and 22 males with the mean age 50.2 + 10.3 years. The mean HbA1c of patients in group with > 6.5% HbA1c was

10.4 + 1.1% whereas the mean HbA1c of the patients in < 6.5% HbA1c group was 5.4 + 0.4%. The duration of illness among T2DM patients with > 6.5% HbA1c was 10.4 + 4.7 years and among patients with HbA1c < 6.5% group was 8.7 + 5.1 years. Whereas no diabetic complications were present in < 6.5% HbA1c group 13 (26%) patients in group with > 6.5% HbA1c had microalbuminuria. Among the group of patients with > 6.5% HbA1c 27 (54%) and in the group with < 6.5% HbA1c 17 (34%) patients were receiving insulin whereas the rest of the patients were on oral hypoglycemic agents. None of the patients or the controls was either a current or ex-smoker. Serum levels of Cu, Zn and Se were measured by inductively coupled plasma-mass spectrometry (ICP-MS) instrument (Perkin-Elmer). After obtaining the informed consent from each patient and control venous blood sample (1 ml) was collected in royal blue tube using aseptic technique. Serum was separated after 30 min of clotting time and samples were kept frozen at -80°C until analysis. A set of five-point calibration standards in 2% supra-pure nitric acid was used. Samples were diluted 1:50 in the same diluent as the corresponding calibration standards. The validity of the results obtained was checked by triple repetition of the analyses.

Statistical analysis

Data were analyzed by MedCalc computer software version 14.8.1. Categorical data were summarized as numbers and percentages. Numeric data were summarized as mean and standard deviation. Comparison between groups was performed using student t test for independent samples and a $p < 0.05$ was considered statistically significant.

Results

Figure 1 compares data for serum levels of Cu, Zn and Se of normal individuals and T2DM patients with < 6.5% HbA1c. The mean serum copper levels among the T2DM patients (13.4 + 4.3 $\mu\text{mol/L}$) and the controls (14.5 + 1.92 $\mu\text{mol/L}$) were not different. The mean Zn level among the T2DM patients (9.9 + 2.7 $\mu\text{mol/L}$) was however significantly lower than the normal controls (15 + 3.2 $\mu\text{mol/L}$; $p < 0.0001$). Similarly, mean Se level among T2DM patients (1 + 0.2 $\mu\text{mol/L}$) was significantly lower than the controls (1.62 + 0.2 $\mu\text{mol/L}$; $p < 0.0004$).

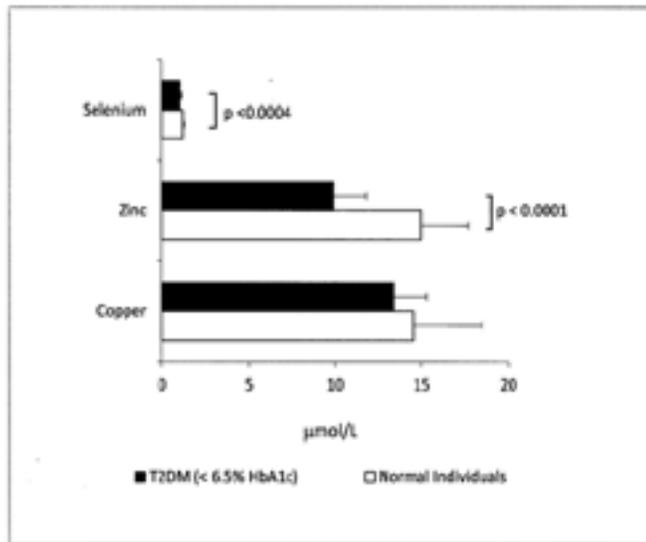


Figure. 1 Comparison of serum levels of trace elements among type 2 diabetes mellitus patients with glycated hemoglobin (HbA1c) of less than 6.5% with normal controls.

Figure 2 shows comparison of serum levels of Zn, Cu and Se between the group of T2DM patients with HbA1c > 6.5% and normal healthy controls. Serum Cu level among T2DM patients (18.1 ± 4.1 μmol/L) was significantly higher than the controls (14.5 ± 1.9 μmol/L; p

< 0.0001). The mean Zn level (15 ± 3.2 μmol/L) among the T2DM patients with HbA1c > 6.5% was also higher than the normal healthy individuals (10.0 ± 3.2 μmol/L; p < 0.009). Similarly, serum Se level of 1.62 ± 0.2 μmol/L among T2DM patients was significantly higher than the normal controls (1.17 ± 0.16 μmol/L; p < 0.0001).

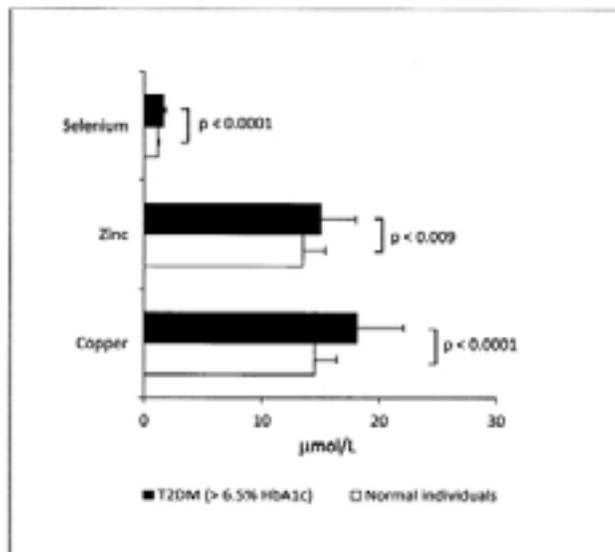


Figure. 2 Comparison of serum levels of trace elements among type 2 diabetes mellitus patients with glycated hemoglobin (HbA1c) of more than 6.5% with normal controls.

Figure 3 shows data for comparison of serum Cu, Zn and Se levels between T2DM patients with HbA1c of greater than and less than 6.5%. The mean Cu, Zn and Se levels among T2DM with HbA1c > 6.5% were consistently higher than the group of patients with T2DM and

HbA1c < 6.5% ($p < 0.0001$). Zn and Cu ratio (Zn/Cu) among the normal individuals was 1.01, among T2DM patients with HbA1c < 6.5% was 1.7 and among T2DM patients with HbA1c > 6.5 was 0.76. HbA1c percentage correlated negatively with Zn/Cu only among patients with T2DM with HbA1c > 6.5% ($r = -0.302$; $p < 0.03$).

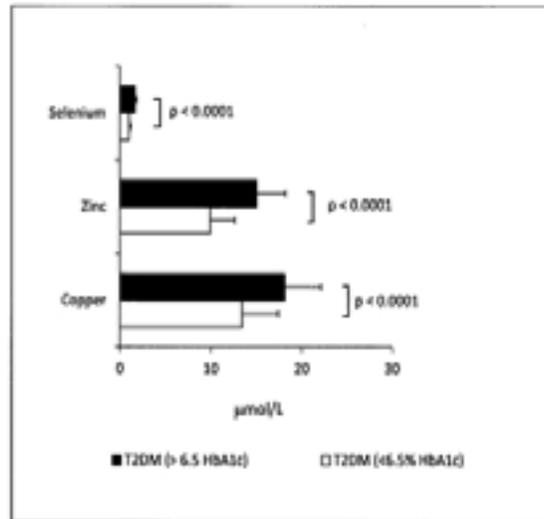


Figure. 3 Comparison of serum levels of trace elements among type 2 diabetes mellitus patients with glycated hemoglobin (HbA1c) of less than 6.5% and more than 6.5%.

Table. Characteristic features of patients with type 2 diabetes mellitus and controls

Variable	HbA1c <6.5% group n = 50	HbA1c >6.5% group n = 50	Control group n = 50
Age \pm sd years	55.4 \pm 6.7	57.8 \pm 14.3	50.2 \pm 10.3
Males	19	17	22
Females	31	33	28
Duration of illness \pm sd years	8.7 \pm 5.1	10.4 \pm 4.7	-
Mean HbA1c%	5.4 \pm 0.4	10.4 \pm 1.1	-
Microalbuminuria n (%)	-	13 (26%)	-
Insulin treatment	17 (34%)	27 (54%)	-
Smokers	-	-	-

Discussion

This study revealed that better glycemic control among T2DM patients was associated with low Zn and Se levels whereas poor glycemic control was associated with elevated levels of Zn, Cu and Se compared to normal individuals. Low blood levels of Zn in T2DM patients observed in the present study are consistent with the previous findings that patients with T2DM tend to have hypozincemia along with the depletion of tissue zinc stores.¹⁶ Increased zincuria observed in diabetes is believed to be secondary to osmotic diuresis and diabetes related polyuria may also contribute to hypozincemia.¹⁷ Zn deficiency has been associated with diabetic complications such as hypertension, thrombosis, ocular involvement, insulin production and resistance to insulin.^{7,18} The main reason for the wide ranging effects of Zn deficiency particularly in diabetes mellitus is due to Zn being a co-factor for over three hundred enzymes involved in various metabolic pathways.¹⁹ Improvement in a number of metabolic parameters following Zn supplementation in T2DM points to the importance of this trace element in pathogenesis of T2DM.²⁰ Despite the existence of a body of evidence describing association of Zn with T2DM the exact role of Zn in the metabolic disorder remains unclear.

Serum levels of Cu were elevated among T2DM patients with poor glycemic control compared to normoglycemic T2DM patients and normal individuals. Increased Cu level among T2DM patients reported previously has been linked with the development of diabetes.^{21,22} Cu is a pro-oxidant and high levels of Cu induce increased production hydrogen peroxide resulting in β cell degeneration and development of T2DM.²³ Zn on the other hand is bestowed with anti-oxidant and anti-inflammatory properties through its ability to down regulate the production of inflammatory cytokines.²⁴ Deficient Zn levels and elevated Cu levels observed in diabetes mellitus therefore tilt the balance in favor of pro-inflammatory milieu. Elevated Cu levels along with reduced ceruloplasmin levels and decreased binding activity of Cu in diabetes leads to elevation of free Cu that is not only toxic but also promotes pro-oxidant activity.²⁵ Hyperglycemia induces protein glycosylation and Cu exhibits increased affinity for these glycosylated proteins resulting in enhanced oxidative stress and production of free radicals predisposing T2DM patients to disease associated complications.²⁶

The negative correlation of Zn/Cu with HbA1c observed in the present study among patients with poor glycemic controls was most likely due to significantly higher level of Cu contributing to reduction of Zn/Cu most likely due to hyperglycemia induced increased free Cu. Negative correlation between HbA1c and Zn/Cu has recently been reported among patients with T2DM.²⁷ Association of high Zn and Cu level with high HbA1c has been reported where high HbA1c percentage tends to exhibit a positive correlation with Cu and a negative correlation with Zn.²⁸ No such correlation was detected in the present study.

Serum Se level was lower among T2DM patients with good glycemic control than the normal individuals whereas higher levels of Se were detected among diabetics with poor glycemic control. Data regarding serum levels of Se among patients with T2DM are inconsistent however low serum level of Se among patients with T2DM has been reported.²⁹ Similarly low levels of Se have also been reported in women with gestational diabetes mellitus.³⁰ Se is an anti-oxidant and provides protection against oxidative stress³¹ that has been implicated in the etiology, pathogenesis and complications of T2DM.³² Deficiency of Se may therefore be a predisposition for development of diabetes. On the contrary long-term supplementation of Se has been linked with increased likelihood of development of T2DM.³³ This was evident in the present study where the group of patients with poor glycemic control had high blood levels of Se. The exact role of Se in the pathogenesis of T2DM remains elusive emphasizing the need for further investigations to gain a better insight regarding Se metabolism in T2DM.

Conclusion

Serum Cu, Zn and Se levels were altered among patients with T2DM compared to the normal healthy controls. Glycemic control among T2DM was observed to influence the blood levels of trace elements where poor glycemic control was associated with significant elevation of Cu, Zn and Se. This study was however limited by small numbers and large-scale studies are recommended to validate the findings of the present study in order to gain a better understanding of trace element homeostasis in T2DM.

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Conflict of interest

None declared.

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