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TRACE MINERAL STATUS RELATED TO LEVELS OF GLYCATED HEMOGLOBIN OF TYPE 2 DIABETIC SUBJECTS IN JEDDAH, SAUDI ARABIA

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SUMMARY: Diabetes mellitus (DM) is of major and increasing global public health importance. People with diabetes are at increased risk of premature disability and death associated with vascular, renal, retinal, and neuropathic complications. Direct association of trace elements in both type 1 and type 2 diabetes has been observed in many research studies. An alteration in the metabolism of these minerals has been demonstrated in diabetes. The aim of the present study was to investigate zinc (Zn), copper (Cu), chromium (Cr), manganese (Mn) and magnesium (Mg) levels in the serum of patients with type 2 diabetes and age-matched healthy subjects and also to assess the association between these elements and glycated hemoglobin (HbA1c). The study population consisted of 55 type 2 diabetic patients and 55 age-matched non-diabetic healthy subjects within the age range of 45–65 years. In this study, we found significantly higher Cu levels ($P < 0.001$), lower Zn levels ($P < 0.05$), and also lower Cr, Mn, Mg levels ($P < 0.05$) in patients with DM in comparison with healthy subjects. Statistical analysis showed a positive correlation between serum levels of Cu and Zn in the group of healthy subjects ($r = 0.97$, $P < 0.0001$). In contrast, we found a negative correlation between these metals ($r = –0.59$, $P < 0.0001$) in patients with DM. We also found significant higher levels of HbA1c ($P < 0.001$) in the DM group than in the healthy group. Positive correlations between levels of HbA1c and Cu ($r = 0.71$, $P < 0.001$) as well as Cr ($r = 0.54$, $P < 0.0001$) and negative correlations between levels of HbA1c and Zn ($r = –0.65$, $P < 0.001$) and also Mg ($r = –.52$, $P < 0.001$) in the DM group were obtained. Patients with DM had altered metabolism of Zn, Cu, Cr, Mn, and Mg, and this may be related to increased values of glycated hemoglobin. We concluded that imbalance in the levels of studied metals may play an important role in the pathogenesis of DM.

Key words: Diabetes mellitus, serum, zinc, copper, chromium, manganese, magnesium, HbA1c.

INTRODUCTION

Type 2 diabetes mellitus (DM) is on track to become one of the major global public health challenges of the 21st century. It accounts for approximately 90 to 95% of all diagnosed cases of diabetes. Patients with type 2 diabetes may have complications like cardiovascular disease, nephropathy, retinopathy, and polyneuropathy. According to WHO report, the prevalence of diabetes in adults worldwide has risen (1,2). The prevalence of DM in Saudi population is high and 90% of diabetic patients suffer from type 2 DM. In

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Saudi Arabia, almost one Saudi in four beyond the age of 30 has DM (3). Some estimate that it will be 40–50% in 2020 (4). Diabetes is more prevalent among Saudis living in urban areas (25.5%) compared to rural Saudis (19.5%) (5).

There is accumulating evidence that the metabolism of several trace elements is altered in DM and that these nutrients might have specific roles in the pathogenesis and progress of this disease (6). Zinc (Zn) is an essential trace metal that is directly involved in the synthesis, storage, secretion, and conformational integrity of insulin monomers and that Zn assembles to a dimeric form for storage and secretion as crystalline insulin (6,7). Lower levels of Zn may affect the ability of pancreatic islet cells responsible for the production and secretion of insulin, such as in type 2 diabetes (6). Epidemiological studies have reported decreased plasma and intracellular Zn concentrations in conjunction with increased urinary Zn excretion in diabetic patients. 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 (6,7).

Copper (Cu) and Zn play a pivotal role in the oxidant/antioxidant mechanism, imbalance of which leads to increased susceptibility to oxidative damage of tissues, thereby leading to the pathogenesis of DM or diabetic complications (8). Cu acts as a pro-oxidant and may participate in metal-catalyzed formation of free radicals. However, Cu and Zn act as structural and catalytic components of some metalloenzymes. Cu is necessary for the catalytic activity of enzymes such as Cu/Zn superoxide dismutase (SOD) that is involved in the protection of cells from superoxide radical. Zn acts as an antioxidant by protecting sulfhydryl groups of proteins and enzymes against free-radical attack in the body (9).

The changes in the metabolism of Cu and Zn that occur during oxidation stress may be important in several processes where oxidative stress is implicated (10, 11). Both the essentiality and toxicity of these metals in the pathogenesis of DM and diabetic complications are often reported (12,13). Some investigators have reported the hypothesis that glycated proteins bind transition metals such as Cu and iron (Fe) and that such glycocholates play an important role in the etiology of peripheral vascular dysfunction and peripheral neuropathies in DM (14).

It was intensively investigated that chromium (Cr) acts as a blood–sugar modulator that could guard against glucose imbalances (15). Insufficient dietary Cr intake has also been implicated as a possible risk factor for the development of diabetes (16). Deficiency of Cr has been shown to predispose a person to glucose intolerance and to promote the development of diabetic complications.

Magnesium (Mg) is the fourth most abundant cation in the body and second in the intracellular environment. It takes part in more than 300 enzymatic reactions (1,2). Deficiency of Mg has been associated with the variety of clinical conditions, including type 2 DM. Mg depletion has a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes (17), as well as on the evolution of complications such as retinopathy, thrombosis and hypertension. Moreover, low serum Mg is a strong independent predictor of the development of type 2 diabetes (18). Recent studies have also indicated that Mg deficiency may be associated with increased oxidative and nitrosative stress through reduction in antioxidants and increased lipid peroxidation (1). Reduced plasma levels of Mg have been documented in both type 1 and type 2 DM, especially in poorly controlled DM (19). The cause of hypomagnesemia was attributed to osmotic renal losses from glycosuria, decreased intestinal absorption, and redistribution of Mg from the plasma into blood cells due to the effects of insulin (17,19).

There are also reports of altered metabolism of other micronutrients such as Fe and manganese (Mn) in diabetes. Mn is a cofactor for a number of enzymatic systems including arginase, which has been found to be elevated in diabetic rats and mice (6). It was suggested that Mn is required for normal insulin synthesis and secretion (6,16).

Diabetes is a free radical associated disease. Investigations carried out in diabetic patients revealed

oxidative stress load (20,21). Oxidative destruction of sub-cellular membrane lipids has been implicated along with other types of intracellular oxidative damage in the normal aging process and in pathophysiology of a number of chronic illnesses. Complex antioxidant mechanism, including antioxidant vitamins and minerals exists to limit the effects of these reactions (20).

DM being a degenerative disease, therefore, may be initiated as a result of peroxidation caused by free radicals. Some trace metals such as Mn, chromium, Cu and vanadium possess antioxidant properties. Deficiency of these metals may thus increase susceptibility to the disease. The development of diabetic late complications (cataract, retinopathy, nephropathy, and neuropathy) is associated with an increased presence of free radicals and therefore elevated oxidative stress of the human body (20). Thus diabetic patients elicit a higher rate of blindness, kidney disease, gangrene, and coronary heart disease several times more than do non-diabetic subjects.

The aim of the present study was to compare the status of some minerals of patients with type 2 DM with non-diabetic healthy subjects and also to assess the association between these elements and glycated hemoglobin (HbA1c).

MATERIALS AND METHODS

Selection of subjects

The study was conducted over a period of two years on the employees of King Abdulaziz University, Jeddah, Saudi Arabia. Patients visited to the university clinic were included in the study. The study population consisted of 55 type 2 diabetic male subjects (DM group) and 55 age-matched non-diabetic male subjects (control group) within age range 45–65 years. Informed consent was sought and obtained from individuals before enrollment into the study. Clearance was obtained from the institutional ethical committee.

Inclusion criteria

Aged 45–65 years; known as type 2 diabetic patients for the past five years; and non-diabetic individuals considering to glucose tolerance test or FBS < 90 mg/dl.

Exclusion criteria

Patients who had diabetes other than type 2 DM, diabetic patients who had been treated with insulin, patients had taken hypotensive diuretics, subjects who had acute complications such as severe infections, major operations, trauma, GI disorders, severe cardiovascular/respiratory disease, patients who were presenting with ketoacidosis, subjects on any concomitant medication such as antioxidant vitamins, minerals, herbal treatment that may interact with glycemic status and oxidative stress parameters, cigarette smokers, and alcoholics were excluded from the study.

Fifty-five apparently healthy non-diabetic subjects of similar socioeconomic status, who were on routine medical checkups in the clinic, were recruited to serve as control. There were no clinical or laboratory disorder in the control group. Body weight and height were measured and used to calculate the body mass index (BMI), which was used as a measure of relative body weight. Following enrollment, both patients and controls were instructed for the following: not to change their lifestyle or their dietary habits and not to take any dietary supplements. The diet was not monitored.

Sample collection and preparation

Fasting blood samples were collected into labled centrifuge tubes, after an 8–12 h overnight fast, from the subjects by venipuncture. The blood samples were centrifuged at 2000 rpm for 10 min using a desktop centrifuge and the serum separated and kept in labeled sample bottles at −70°C until further analysis.

Instrumention

The sera were analyzed for HbA1c and FBG using an autoanalyzer (Roche Modular P-800, Germany). The concentration of trace elements of each sample was measured by Graphite Furnace Atomic Absorption spectrometer (VARIAN, Model Spectra AA 30P) using calibration method. The accuracy of determination was evaluated by measuring the metal contents of certified biological reference materials (Seronorm Trace Elements Serum; Nycomed Pharma, Oslo, Norway).

Statistical analysis

Results were presented as mean standard deviation. The significance of difference in the trace elements level in samples between two groups was tested using t-test analysis. Association between variables was determined using the Pearson correlation analysis on Microsoft Excel and SPSS software version 16. A two-sided p value <0.05 and <0.01 was considered statistically significant for the t-test and Pearson correlation analysis, respectively.

Tablo 1: The serum levels of Zn, Cu, Cr, Mn, and Mg and Cu/Zn ratio in the DM group and the control group of healthy subjects.

Parameters	DM group	Control group	P value
N	55	55	
Sex	Male	Male	
Age (y)	60.09 ± 6.79	58.92 ± 7.26	<0.05
Duration of diabetes(y)	5.33 ± 3.26		
BMI (kg/m^2)	29.79 ± 1.72	24.37 ± 1.58	<0.05
Fasting blood glucose(mmol/L)	10.21 ± 3.56	4.23 ± 0.15	<0.05
HbA1c (%)	9.18 ± 2.30	5.27 ± 1.28	<0.001
Zn (μg / dl)	96.25 ± 24.32	130.20 ± 32.04	<0.05
Cu (μg / dl)	143.13 ± 30.61	121.28 ± 19.76	<0.001
Cr (μg / dl)	4.13 ± 0.52	6.31 ± 0.42	<0.05
Mn (μg / dl)	3.37 ± 0.38	4.93 ± 0.46	<0. 05
Mg (μg / dl)	17.76 ± 0.96	22.93 ± 1.73	<0.05
Cu/Zn ratio	1.38 ± 0.42	1.12 ± 0.17	<0.001

P value between the DM group and the control group; mean values are given as mean ± standard deviation.

RESULTS

Baseline characteristics of patients with DM (DM group) and healthy subjects (control group) as well as serum concentrations of Zn, Cu, Cr, Mn, and Mg and the Cu/Zn ratio are shown in Table 1.

The mean age of diabetic patients was 60.09 versus 58.92 years of non-diabetic subjects. The diabetic patients were generally heavier than the control subjects (Table 1). The results of the BMI indicated that the diabetic subjects were overweight. There was significant difference in the BMI of the diabetic patient when compared with the control group. Fasting blood glucose and HbA1c were significantly higher in diabetic patients than in non-diabetic subjects (Table 1).

We found significantly higher Cu levels ($p < 0.001$), lower Zn levels ($p < 0.05$), higher values of Cu/Zn ratio ($p < 0.001$), and also lower Cr, Mn, and Mg levels ($p < 0.05$) in patients with DM in comparison with healthy subjects. Sixty percent of patients with DM had serum levels of HbA1c lower than 8% (6%–8%). Glycated hemoglobin levels higher than 8% (8%–13.2%) were present in 40% of diabetic patients.

We evaluated levels of Cu, Zn, Cu/Zn ratio, Cr, and Mg separately for reasonably controlled diabetes (HbA1c levels < 8%) and also for poorly controlled diabetes (HbA1c levels > 8%). The difference between the group with HbA1c levels less than 8% and the group with HbA1c greater than 8% were obtained. We found that the group with HbA1c levels greater than 8% ($n = 22$) had significantly increased levels of Cu ($p < 0.001$), Cr ($p < 0.0001$), and Cu/Zn ratio ($p < 0.001$) and decreased levels of Zn ($p < 0.0001$) and Mg ($p < 0.001$) when compared with the group with HbA1c less than 8% ($n = 33$).

We calculated associations between levels of HbA1c and metal concentrations in both groups. Positive correlations between levels of HbA1c and Cu ($r = 0.51$, $P = 0.002$), Cr ($r = 0.49$, $P = 0.004$), as well as Cu/Zn ratio ($r = 0.62$, $P = 0.006$) and negative correlations between levels of HbA1c and Zn ($r = -0.48$, $P = 0.01$) and also Mg ($r = -0.46$, $P = 0.015$) in both groups were obtained.

We calculated association between individual concentrations of metals and Cu/Zn ratio. An imbalance in the levels of Cu and Zn was found in patients with DM when compared with the control group. Statistical analysis showed a positive correlation between

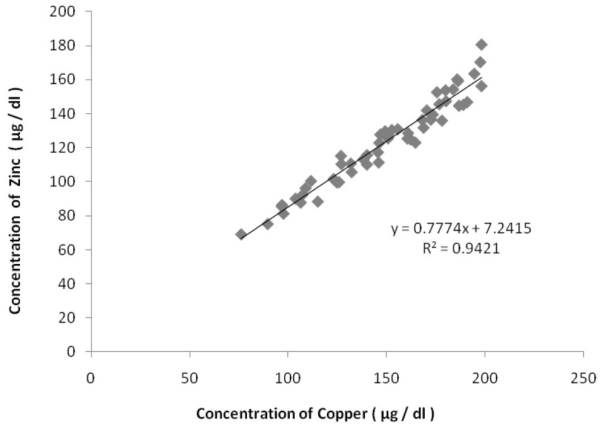

Figure 1: Correlation between serum levels of Cu and Zn in the control group of healthy subjects

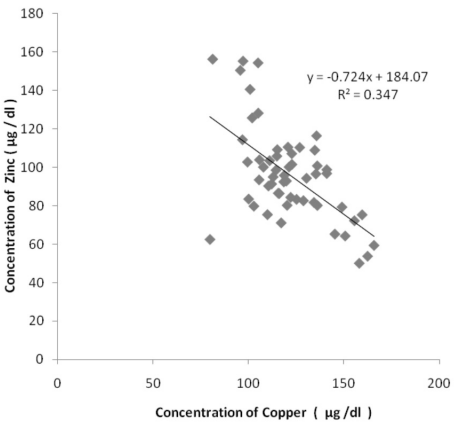

Figure 2: Correlation between serum levels of Cu and Zn in patients with diabetes mellitus

serum levels of Cu and Zn in the group of healthy subjects (r=0.97, P<0.0001) (Figure 1). In contrast, we found a negative correlation between these metals (r = –0.59, P < 0.0001) in the patients with DM (Figure 2).

The association between HbA1c and serum concentrations of Cu, Zn, Cr, Mn, and Mg and the Cu/Zn ratio were also evaluated. A positive correlation between serum levels of HbA1c and Cu in the DM group (r = 0.71, p < 0.001) is shown in Figure 3. There is also a positive correlation between HbA1c and Cu/Zn ratio (r = 0.673, p < 0.001). Again we found a positive correlation between levels of HbA1c and Cr in the DM group (r = 0.54, p < 0.0001) (Figure 4). We recorded a negative correlation between serum levels of HbA1c and Zn (r = –0.65, p < 0.001) as well as between HbA1c and Mg (r = –0.52, p < 0.001) in patients with DM (Figures 5 and 6). We found no significant correlation between serum levels of HbA1c and Mn in the DM group.

DISCUSSION

Trace elements have been accepted as essential for optimum health. The significance of trace elements in normal growth, development, and overall body

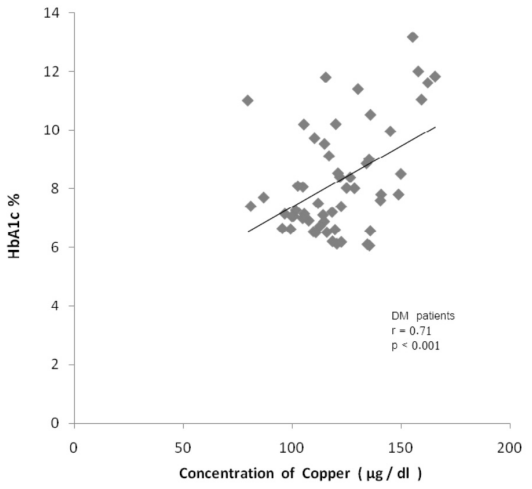

Figure 3: Correlation between HbA1c and Cu in patients with diabetes mellitus

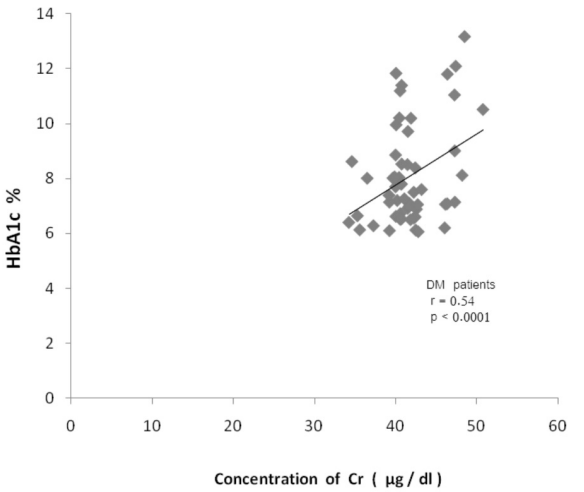

Figure 4: Correlation between HbA1c and Cr in patients with diabetes mellitus

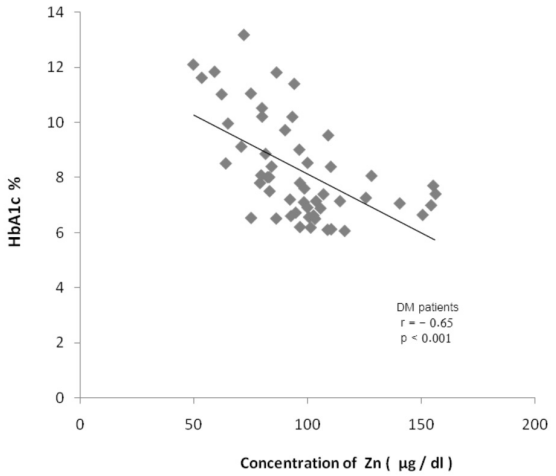

Figure 5: Correlation between HbA1c and Zn in patients with diabetes mellitus

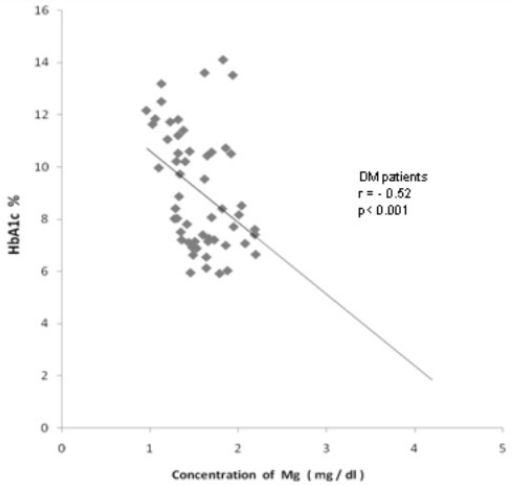

Figure 6: Correlation between HbA1c and Mg in patients with diabetes mellitus

metabolism cannot be overemphasized. There is, however, an accumulating evidence that the metabolism of several trace elements is altered in DM (6,19–22). Some of these trace elements act as antioxidants and prevent membrane peroxidation. The beta cells of the pancreas, the cells that produce insulin, are sensitive to oxidative stress. This is due largely to the fact that their intracellular antioxidant defense mechanisms are weak compared to liver tissues (23). Oxidative stress is thus suggested to be a potential contributor to the development of DM and the associated complications (24). This may not be unconnected to the fact that the antioxidant status including antioxidant mineral elements may be inadequate in diabetic subjects. The metabolic significance of the evaluation of antioxidants in diabetic patients is therefore of paramount importance. In addition to the antioxidant roles of some of these mineral elements, they may act directly on glucose metabolism.

The results of the current work indicated an imbalance in the levels of trace elements in type 2 DM. We found significantly higher levels of Cu and Cu/Zn ratio and significantly reduced the levels of Zn and Mg in patients with DM when compared with healthy subjects (Table 1). The serum level of Cu was positively correlated with that of Zn in the group of healthy subjects (Figure 1). In contrast, we found a negative correlation between the levels of Cu and Zn in patients with DM (Figure 2). Consequently, we may suggest that the imbalance in the levels of studied metals may play an important role in the pathogenesis of DM.

Several previous studies have suggested that metabolic disturbances associated with insulin resistance and hyperglycemia can cause the deficiency of some minerals (6,25,26). Deficiency of Zn and Mg has been frequently reported in DM as a contributing factor to the etiology of diabetic complications such as hypertension, retinopathy, and thrombosis (6,8,17,27). In our study, decreased Zn levels were associated with increased Cu levels in patients with DM, as shown in Figure 2. True prevalence of Zn and Mg deficiency among patients with DM is still under discussion in the literature (19,28,29). Zn and Mg deficiency might be related to differences in the important factors regulating homeostasis of these metals such as gastrointestinal absorption and urinary excretion.

Recent studies have established (9,17,30) that the serum levels of some minerals are lower in patients with DM than those in healthy subjects, especially in poorly controlled diabetes. Increased urinary excretion of Zn and Mg due to hyperglycemia and osmotic diuresis may contribute to reduced levels of these elements. Because deficiency of Zn and Mg may be attributed to the use of diuretics (26), diabetic patients taking hypotensive

diuretics were excluded from the study. Osmotic diuresis clearly accounts for a portion of the Mg loss (31). It is believed that glycosuria that accompanies the diabetic state impairs renal tubular reabsorption of Mg from glomerular filtrate (32). Renal Mg handling may be modulated by insulin even in non-diabetic individuals; administration of insulin increases urinary Mg excretion rate—a rise in Mg excretion rates in diabetic patients with increasing insulin dosage has been implicated in the hypomagnesemia seen in diabetic patients (32). Studies have demonstrated that insulin regulates the intracellular Mg concentration by stimulating the plasma membrane ATPase pumps and increasing free Mg entry into the cells (32–34), so the low serum magnesium levels seen in the diabetic population may be a consequence of insulin resistance. Dietary Mg intake and intestinal hypoabsorption may also be a factor in the low serum Mg levels of diabetic patients.

The results of our study indicate that the alterations in the serum levels of Cu, Zn, Cr, and Mg and in Cu/Zn ratio in patients with DM are associated with the increased levels of HbA1c. We found that HbA1c levels were positively correlated with Cu (Figure 3) and Cr (Figure 4) as well as Cu/Zn ratio and inversely correlated with Zn and Mg (Figures 5 and 6).

In our study, we also determine the impact of the increased levels of HbA1c on the levels of Cu, Zn, Cu/Zn ratio, Cr, and Mg. We found differences between the group with HbA1c levels less than 8% and the group with HbA1c levels greater than 8%. On the basis of our results, we can suggest that in the patients with poorly controlled diabetes exists a strong relation between the increased levels of HbA1c and the altered levels of Zn, Cu, Cr, and Mg. These patients are at increased risk for development of diabetic complications. Our findings also support several studies (9,11,19,27,33) based on the hypothesis that long-term hyperglycemia is considered to be a risk factor of diabetic complications and is associated with impaired status of some minerals.

It has been reported by some authors (27,35) that Zn deficiency is associated with reduced insulin secretion and increased tissue resistance to insulin action. Our study showed that the reduced levels of Zn were present in 60% of type 2 DM patients who had serum levels of HbA1c higher than 8%. We also found that reduced Mg levels were present in 60% of type 2 DM patients with HbA1c levels higher than 8%. In accordance with some studies (8,17,25,32), we can speculate that patients with type 2 DM, especially those with poor metabolic control, are at increased risk of Zn, Cr, and Mg deficiency. Poorly controlled DM may cause the alterations in the homeostasis of these metals.

Several reports have indicated (6,19,27,36) that the metabolism of some trace elements such as Cu and Zn is altered in DM and that these alterations might be a contributing factor in the pathogenesis of this disease. It has been also suggested (8,19) that hyperglycemia and hyperinsulinemia increase the production of free radicals and decrease the efficiency of antioxidant defense systems. It is well known that Cu and Zn play a vital role in oxidative stress (9). Therefore, changes in the levels of Cu and Zn and Cu/Zn ratio may influence the equilibrium in the antioxidant defense system and enhance the toxic effect of metal-dependent free radicals. These associations may in this way initiate and potentiate the pathogenetic processes leading to diabetic complications (12,30,37). Cu and Zn are needed for essential activity of antioxidant enzyme Cu/Zn SOD. SOD catalyzes dismutation of superoxide radical into hydrogen peroxide. Therefore, abnormal metabolism of Cu and Zn may affect the function of SOD and result in decreased protection of cells from superoxide radical. Moreover, under conditions of hyperglycemia, glycated proteins exhibit increased affinity to Cu ions and may result in glycocholates formation. The glycocholates can be accumulated in the endothelium and participate in redox reactions. Therefore, alterations in the metabolism of Cu can be an important contributing factor for the progression of diabetic vascular complications (13,36).

The results of the present work indicated that almost all the diabetic subjects showed Cr deficiency. The implication of this finding cannot be overemphasized. Hyperglycemia and high levels of insulin increase chromium excretion (32), so the low serum levels of Cr

seen in the diabetic patients has been attributed to insulin resistance, hyperglycemia, and osmotic diuresis resulting from glycosuria, which increase urine Cr excretion (32,38–40). Cr has been reported to increase insulin binding to cells and number of insulin receptors, and activates insulin receptor kinase leading to increase in insulin sensitivity (38). Trivalent Cr acts as a cofactor for insulin and is an integral part of the cellular response to this hormone (21). Accordingly severe Cr deficiency was implicated to cause impaired glucose tolerance and subsequent hyperglycemia and glycosuria (38). Baker and Campbell (39) also reported an association between Cr deficiency on one hand and hyperinsulinemia, diabetic neuropathies, or vascular pathologies on the other. Cr, which is a component of glucose tolerance factor (21,43), is also known to inhibit tyrosine phosphatase, an enzyme responsible for the termination of insulin receptor response (40). Cr was reported to raise plasma HDL cholesterol and HDL:LDL ratio (21).

The serum Mn level of diabetic subjects in the current work was significantly ($p < 0.0001$) different from the value obtained for the control subjects. The percentage of diabetic subjects with Mn deficiency was however lower compared to the subjects with Cr deficiency. Mn has been shown to be important in insulin synthesis and secretion (41). It has been shown that type 2 diabetic subjects responded well to oral doses of Mn (42). Mn is a cofactor of many enzymes including mitochondrial SOD (43). Mn-activated enzymes play important roles in the metabolism of carbohydrates, amino acids, and cholesterol (44). There are conflicting reports of Mn deficiency in DM (21,44). Diabetic patients with the higher blood levels of Mn were reported to be better protected from oxidation of LDL cholesterol. LDL oxidation contributes to the development of intra-arterial plaque, which can lead to heart attack and stroke (45). Diabetic patients with liver diseases have been reported to excrete more Mn than those without liver problems (46).

Generally, some mineral elements (Cr, Mn, and Mg) have been reported to be excreted at higher than normal rates in patients with DM (46). This may not be unconnected to the hyperglycemia-mediated polyuria in the patients. Consequently there is a decrease in the plasma levels of the elements in these subjects. This may predispose the subjects to further oxidative onslaught and decrease glucose tolerance, leading ultimately to the development of late complications of DM. It may therefore be pertinent to suggest the evaluation of inclusion of dietary supplementation of these mineral elements in the management of DM.

The BMI and fasting blood glucose were significantly higher in the diabetic population when compared to the non-diabetic population of the study. It has been established that diabetic patients have higher levels of fasting blood glucose, glycated hemoglobin and lipoproteins than non-diabetic patients (47–49).The higher levels of fasting blood glucose seen in diabetic patients are a result of insulin deficiency or insulin resistance associated with DM (32,50).

In conclusion, the present results demonstrate that there is an imbalance in the levels of some trace elements such as Cu and Zn among patients with DM in comparison with healthy subjects. These changes may play an important role in the pathogenesis of this disease by the participation of these elements in the oxidative stress. We have also shown that the increased levels of Cu and Cu/Zn ratio and the decreased levels of Zn, Cr, and Mg are associated with increased values of HbA1c in diabetic patients. These findings may contribute to explaining the role of impaired metabolism of some mineral elements in the pathogenesis of diabetes. We conclude that impaired metabolism of Cu, Zn, Cr, and Mg may be suggested as a contributing factor in the progression of DM and also in the development of diabetic complications.

The present study provides significant evidence showing that altered metabolism of Cu, Zn, Cr, and Mg is strongly associated with the increased levels of HbA1c. These associations might represent a risk factor for the development of diabetic complications. Our findings indicate that it is necessary to take into consideration possible changes in the metabolism of these metals, mainly their associations with long-term hyperglycemia.

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