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THE ASSOCIATION BETWEEN SERUM GLUCOSE AND SERUM LEAD AND SELECTED TRACE ELEMENTS IN TYPE 2 DIABETES MELLITUS PATIENTS IN JEDDAH, SAUDI ARABIA

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SUMMARY: Diabetes mellitus (DM) is a chronic metabolic disorder affecting carbohydrate, lipid, and protein metabolism. A number of studies have reported an association between DM and alterations in the metabolism of several trace minerals. In this study, serum zinc (Zn), chromium (Cr), manganese(Mn), magnesium (Mg), and lead (Pb) were estimated in 55 diabetic patients attending the clinic of King Abdulaziz University, Jeddah (Saudi Arabia), and the results were compared with those of apparently healthy, nondiabetic volunteers of comparable age and social status. The serum glucose level of diabetic subjects (10.21 ± 3.56 mmol L-1) was significantly ($p < 0.05$) higher than the value obtained for the nondiabetic subjects (4.23 ± 0.15 mmol L-1). The mean serum levels of Zn (96.25 ± 24.32 µg/dl), Cr (4.13 ± 0.52 µg/dl), Mn (3.37 ± 0.38 µg/dl), and Mg (17.76 ± 0.96 µg/dl) were significantly ($p < 0.05$) lowered in diabetic subjects. The mean serum Pb level of diabetic patients was (17.38 ± 5.06 µg/dl) and significantly higher ($p < 0.05$) than that of control subjects. In the present study, the age of the diabetic patients did not show any significant correlation with serum glucose ($r = 0.124$). The serum levels of glucose were found negatively correlated with serum levels of Zn, Cr, Mn, and Mg of diabetic subjects. A positive relationship was observed between concentrations of serum glucose and Pb ($r = 0.438$, $p < 0.01$). The low serum levels of Zn, Cr, Mn, and Mg in diabetic patients compared to that of control subjects may be due to the poor glycemic control.

Key words: Diabetes mellitus, serum, zinc, chromium, manganese, magnesium, lead, fasting serum glucose.

INTRODUCTION

Trace elements form part of our daily diet, which are well known to play vitally important roles in the maintenance of health (1). Now a days, composition of our diet has changed considerably, which causes greatly increased incidence of many different diseases such as diabetes mellitus (DM) (2). According to some studies, trace element concentrations are different in serum and urine of diabetic patients and the healthy population (3,4). Diabetes is estimated to afflict about 366 million people world-wide in 2011 and this represents about 8.3% of the world's population; by 2030 this is expected to rise to 552 million (5,6). Type 2 diabetes comprises 90% of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity (5,6). Today, the Arab world is severely affected by this disease. Almost 50% of people aged 40-59 are

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thought to be suffering from diabetes (7), and in the Arab world, more than 24% of the Qatar's population is believed to be diabetic (7). The prevalence of DM in the Saudi population is high, and 90% of them suffer from type 2 DM. In Saudi Arabia, almost one Saudi in four beyond the age of 30 has DM (8). Some estimate that it will be 40%-50% in 2020 (9). Diabetes is more prevalent among Saudis living in urban areas (25.5%) than those living in rural areas (19.5%) (10).

DM is a chronic disorder of carbohydrates, lipids, and protein metabolism. There is defective or deficient insulin secretion, which results in impaired carbohydrate metabolism. This is the characteristic feature of diabetes mellitus, which results in hyperglycemia. DM is a heterogeneous disease characterized by an absolute or relative deficiency of insulin and insulin resistance. Numerous authors have evaluated mineral levels and status in diabetic subjects, yet, often inconsistent and contradictory results have been presented (11-15). This difference may be due to the number of subjects, sex, and laboratory processing. Some trace elements act as antioxidants and prevent membrane peroxidation, while others act directly on glucose metabolism (11).

Literature surveys show that some trace elements such as chromium (Cr), magnesium (Mg), zinc (Zn), manganese (Mn), molybdenum (Mb), and selenium (Se) play an important role in insulin action, including activation of insulin receptor sites (16), serving as cofactors or components for enzyme systems involved in glucose metabolism (17), increasing insulin sensitivity, and acting as antioxidants preventing tissue peroxidation (18). Alternatively, homeostasis of trace elements can be disrupted by DM (16,19). Deficiencies of certain minerals such as Mg, Zn, and Cr predispose to glucose intolerance and promote the development of diabetic complications such as retinopathy, thrombosis, and hypertension (16,20), impaired repair of tissues and wound healing (16,21), and diabetic angiopathy (16). Reduction of trace element stores might be responsible for various adverse clinical effects even with normal serum trace element concentration (16).

Zn is an essential micronutrient, which has an important role in the functioning of hundreds of enzymes in insulin metabolism and acts as an efficient antioxidant (22,23). Concerning metabolic diseases (insulin resistance, metabolic syndrome, diabetes), Zn is important because it plays a role in the stabilization of insulin hexamers, pancreatic storage of the hormone, and is an efficient antioxidant, while oxidation is considered to be a main component in initiation and progression of insulin resistance and diabetes (24).

The trace element Cr increases insulin binding to cells by increasing insulin receptor numbers, and it may lead to increased insulin sensitivity, glucose utilization, and beta-cell sensitivity (25). Cr supplements improve glucose tolerance in people with type 2 diabetes mellitus.

Mn plays an important role in a number of physiologic processes, and as a constituent of some enzymes and an activator of different enzymes (26). These Mn-activated enzymes play an important role in the metabolism of carbohydrates, amino acids, and cholesterol.

Mn superoxide dismutase (MnSOD) is the principal antioxidant enzyme of the mitochondria. Because mitochondria consume over 90% of the oxygen used by cells, they are especially vulnerable to oxidative stress. The peroxide radical is one of the reactive oxygen species produced in mitochondria during ATP synthesis. MnSOD catalyzes the conversion of superoxide radicals to hydrogen peroxide, which can be reduced to water by other antioxidant enzymes (26).

Mn deficiency has been observed in a number of animal species. Signs of Mn deficiency include impaired growth, impaired reproductive function, skeletal abnormalities, impaired glucose tolerance, and altered carbohydrate and lipid metabolism. In humans, demonstration of Mn deficiency syndrome has been less clear (26). Deficiency of Mn or low levels of Mn in blood or tissue has been associated with several chronic diseases like osteoporosis, epilepsy, and DM (26). As oxidative stress is a reason for the development of diabetic complications, it would be important to study the concentrations of Mn in the serum of diabetic patients.

Mg is an essential ion involved in glucose homeostasis at multiple levels. It is a cofactor in the glucose transport system of hepatocyte plasma membranes, and it regulates hepatocyte mitochondrial functions. It catalyzes the various enzymes involved in the phosphorylation of glucose in its anaerobic metabolism, as well as, in its oxidative decarboxylation in the citric acid cycle and can modulate the mechanism of energy transfer from high-energy phosphate bonds. Mg also plays a role in the release of insulin and the maintenance of pancreatic beta-cell cycle (27). It can presumably increase the affinity and, moreover, the number of insulin receptors. In physiological doses, Mg administration does not modify plasma glucose, but pharmacological doses of Mg cause hyperglycemia through increased adrenaline release along with a decrease in insulin secretion (27). In experimental animals, severe and prolonged Mg deficiency caused exhaustion and loss of β-cells in the pancreas. However, insulin acts as an Mg-sparing hormone, both directly and indirectly by stimulating vitamin D hydroxylation. It also enhances the shift of Mg from the extracellular space into hepatocytes and muscle cells (27). It has been shown that the main action of insulin on target tissues involves an inophore effect on Mg and calcium. The translocation of Mg seems particularly correlated to the peptide mediator and to trans-phosphorylation reactions. Insulin deficiency induces a drop in 1,25-dihydroxycholecalciferol and modifies the secretion of parathyroid, calcitonin, and gastrointestinal tract peptide hormones; which in turn favor the occurrence of Mg depletion (27).

Lead (Pb) is a heavy metal that is dangerous to most of the human body's organ systems and interferes with body metabolism and cellular functions. It produces damaging effects in the hematopoietic, hematic, renal, reproductive, and gastrointestinal systems (28). Pb has been investigated in many pathological conditions, and the level of this metal in this environment is of great concern. Environmental Pb exposure is a risk factor for Pb nephropathy (29). Low-level environmental Pb exposure has been shown to contribute to Pb nephropathy even at blood Pb levels below 5 μg/dl, especially in susceptible populations like hypertensive and diabetic patients (29). Therefore, populations with higher environmental Pb exposure are at a higher risk for Pb nephropathy. Occupational Pb exposure is an important pathway for Pb exposure and a sufficient risk factor for the development of Pb nephropathy, as various studies have shown a significant association of renal impairment among Pb workers compared to controls (29).

In recent years, there has been a growing understanding of the role of minerals, in particular, Zn, Cr, Mn, and Mg in diabetes. Overall, available studies on the role of minerals in diabetes suggest deficiency of Zn, Cr, Mn, and Mg in type 2 diabetic patients. Thus, the present study was conducted to investigate the fasting serum Zn, Cr, Mn, Mg, and glucose in DM subjects, and the results were compared with those of apparently healthy nondiabetic subjects of comparable socioeconomic status. The serum levels of Zn, Cr, Mn, Mg, and glucose were correlated in type 2 diabetic subjects to determine the relation of mineral nutritional status to the hyperglycemia.

MATERIALS AND METHODS

Selection of subjects

The study was conducted over a period of 2 years on the employees of King Abdulaziz University, Jeddah, Saudi Arabia. Patients who visited 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, nondiabetic male subjects (control group) within an 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 type 2 diabetic patients for the past five years, and nondiabetic patients, considering a glucose tolerance test or FBS < 5 mmol L-1.

Exclusion criteria

Patients who had diabetes other than type 2 diabetes mellitus; diabetic patients who had been treated with insulin; patients who had taken hypotensive diuretics; subjects who had acute complications such as severe infections, major operations, trauma, GI disorders, and severe cardiovascular/respiratory disease; patients who presented with ketoacidosis; subjects on any concomitant medication such as antioxidant vitamins, minerals, and 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, nondiabetic 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 disorders 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 not to change their lifestyle or their dietary habits and not to take any dietary supplements. The diet was not monitored.

Table 1: Mean serum levels of glucose, Zn, Cr, Mn, Mg, and Pb in diabetic patients and control subjects.

Parameters	Control	Diabetic patients
N	55	55
Age of subjects (year)	58.92 ± 7.26	60.09 ± 6.79*
Duration of diabetes (year)	1.33	3.26*
BMI (kg/m2)	24.37 ± 1.58	29.79 ± 1.72*
Fasting serum glucose (mmol/L)	4.23 ± 0.15	10..21 ± 3.56*
Zn (μg/dl)	130.20 ± 32.04	96.25 ± 24.32*
Cr (μg/dl)	6.31 ± 0.42	4.13 ± 0.52*
Mn (μg/dl)	4.93 ± 0.46	3.37 ± 0.38*
Mg (μg/dl)	22.93 ± 1.73	17.76 ± 0.96*
Pb (μg/dl)	11.05 ± 2.11	17.38 ± 5.06 *

*Significant at p < 0.05; mean values are given as mean ± standard deviation.

Sample collection and preparation

Fasting blood samples were collected into labeled 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 was separated and kept in labeled sample bottles at -70°C until further analysis.

Instrumention

The sera were analyzed for fasting serum glucose using an auto-analyzer (Roche Modular P-800, Germany). The trace elements concentration of each sample was measured by Graphite Furnace Atomic Absorption Spectrometer.

Statistical analysis

Results were presented as mean standard deviation. The data was analyzed with the help of an independent "t" test and Pearson's correlation. The differences between the diabetic and control groups with respect to serum levels of glucose, Zn, Cr, Mn, Mg, and Pb were tested by using an independent "t" test. The interrelationship between serum levels of glucose with serum levels of Zn, Cr, Mn, Mg, and Pb in diabetic subjects was assessed by using Pearson's correlation.

RESULTS

This study was conducted on 55 patients with DM type 2 and on 55 normal healthy subjects. All the diabetic patients and healthy subjects were married. The age, duration of diabetes, BMI, and fasting serum glucose of patients with DM group and healthy subjects (control group) as well as serum concentrations of Zn, Cr, Mn, Mg, and Pb are shown in Table 1. The mean age of the diabetic patients was 60.09 ± 6.79 years and for nondiabetic healthy controls was 58.92 ± 7.26 years. The results of the BMI indicated that the diabetic subjects were overweight. There was significant difference ($p < 0.05$) in the BMI of the DM group when compared with that of the control group.

Fasting serum glucose was significantly ($p < 0.05$) higher in diabetic patients than in nondiabetic subjects.

We found significantly higher Pb levels ($p < 0.05$) and lower Zn, Cr, Mn, and Mg levels ($p < 0.05$) in patients with DM in comparison with healthy subjects.

In diabetic patients, the serum glucose levels significantly correlated negatively with the serum concentrations of Zn, Cr, Mn, and Mg. Correlation curves for Zn and Mg with serum glucose levels are shown in Figures 1 and 2. The correlation curves for Cr and Mn with serum glucose were also drawn but they are not shown here. A significant positive relationship was observed between fasting serum glucose and Pb concentrations ($r = 0.438$, $P < 0.01$) in patients with DM (Figure 3).

Table 2 shows significant negative correlation coefficients between serum glucose and the elemental concentrations of diabetic patients.

DISCUSSION

Diabetes has become an international health-care crisis that requires new approaches for prevention and treatment. Diabetes management should begin with exercise and diet (15,30,31). From the rigidly controlled semi-starvation diets in ancient times, through to the 70%:20%:10% diet (for fat, protein, and carbohydrate,

Table 2: Correlation coefficients (r) of serum glucose with serum Zn, Cr, Mn, Mg, and Pb of type 2 diabetic subjects.

Independent variable	Correlation coefficient (r)
Zn	- 0.316*
Cr	- 0.362*
Mn	- 0.308*
Mg	-0.427*
Pb	0.438**

*Correlation is significant at $p < 0.05$/
**Correlation is significant at $p < 0.01$.

respectively), to the present "all-food-can-fit" regimens, we have arrived at nutrition science as we know it today – "medical nutrition therapy" (31). Dietary modification, the simplest and cheapest form of diabetes treatment, is the primary therapy in type 2 diabetes (32).

In reviewing clinical studies published on this topic over the last few years, it becomes apparent that several minerals are of great importance and hence their potential impact on the typical diabetic individuals. The minerals found to be subjects of concern in diabetic patients most commonly are: Mg, Zn, Cr, and Cu. Alteration in the status of these trace elements has been reported in a number of disease states, trauma, and infections. Diseases of liver and kidney have been known to affect tissue distribution and excretion of trace elements (33). Excessive accumulation or depletion of trace elements may have significant clinical implication, including increase risk of cancer, cardiovascular disease, immune deficiency anemia, renal function impairment, and bone disease (34). The actual status of these elements in DM and other ailments is still uncertain. A number of signs and symptoms of diabetes are shared in common with different trace elements' deficiencies. These include impaired glucose tolerance, fasting hyperglycemia, glycosuria, hypoglycemia, elevated circulating insulin, nephropathy, and peripheral neuropathy (34).

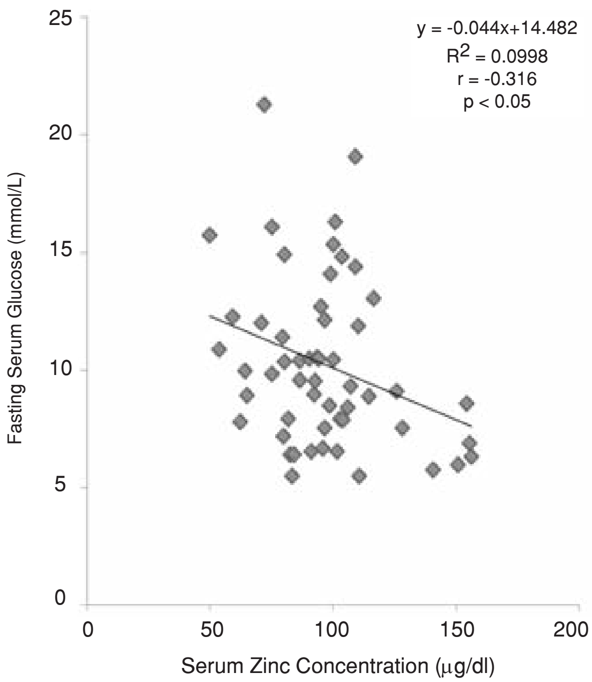

Figure 1: Correlation between zinc concentration and fasting serum glucose in type 2 diabetic patients.

In the present study, fasting serum glucose level was significantly higher in diabetic patients than in nondiabetic healthy controls. It has now been established by different authors (11-16,35,36) that diabetic patients have significantly higher levels of fasting serum glucose than those of the control groups.

Diabetes has been shown to be associated with abnormalities in the metabolism of Cr, Zn, and Mg. Impairment of Cr, Zn, and Mg status has been reported as aggravating factors in the progression of diabetes. Present study reports that there is a significant decrease in serum concentrations when compared to controls. This decreased serum Cr levels in diabetic patients than in controls has been well described in earlier studies (13-16). Cr is a cofactor in the action of insulin and it potentiates the action of insulin (15). As such it may improve blood glucose levels in individuals with a tendency toward blood glucose fluctuations associated with diabetes (hyperglycemia). Thus, it may not be surprising to find (as noted in this study) an inverse relationship between serum Cr levels and blood glucose control.

In the present study, the serum Zn level of the patients with DM type 2 is lesser than of the controls. This has been proposed that the decreased serum Zn level is due to its complex formation with insulin and hence the lack of free insulin enhances the appearance of the symptoms of diabetes that occurred in these patients (15). Zn is involved in many biological processes including catalysis,

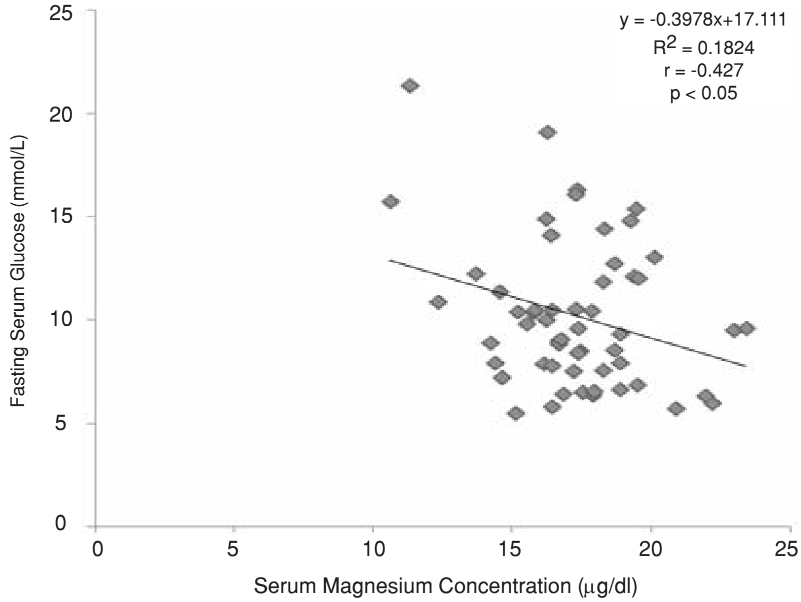

Figure 2: Correlation between magnesium concentration and fasting serum glucose in type 2 diabetic patients.

stabilization of cell membrane, and regulation of gene expression, and influences many metabolic functions (16). Zn has insulin-like effects that cause enhanced glucose uptake by inhibiting glycogen synthesis (16).

Low serum levels of Zn in diabetic patients are in accordance with those reported by several research groups (12,15,16). The low gastrointestinal absorption and high urinary excretion of Zn in diabetic patients may explain hypoz-

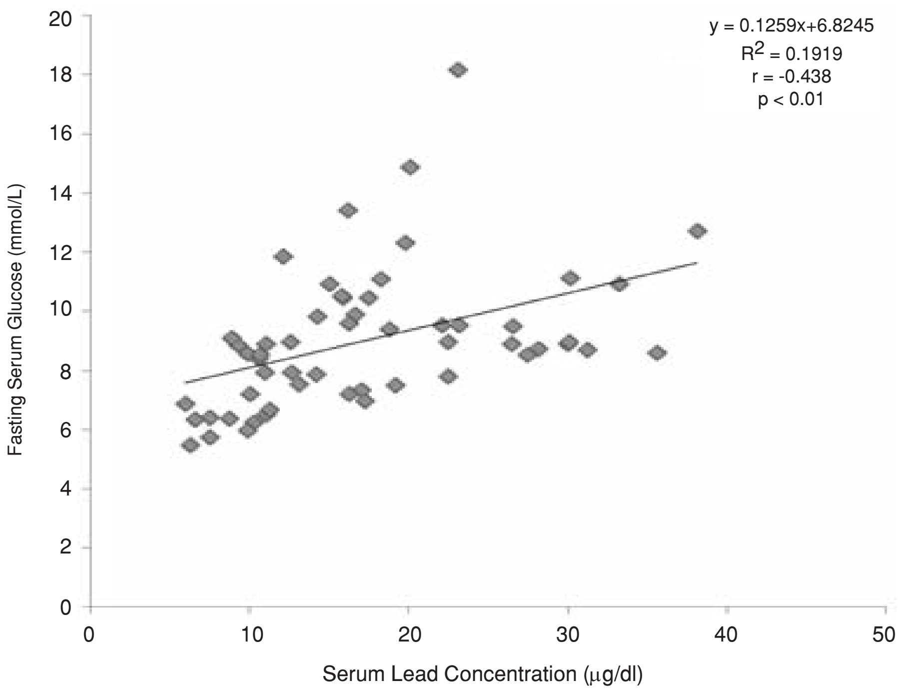

Figure 3: Correlation between Pb concentration and fasting serum glucose in type 2 diabetic patients.

incemia seen in the DM group (16). Hyperzincuria may be a result of hyperglycemia than any specific effect of endogenous or exogenous insulin on the renal tubules. Hyperglycemia has been postulated to interfere with the active transport of Zn back into the tubular cells (16).

Zn and insulin concentrations in the pancreas change in the same direction in a variety of situations in humans (15). Zn is useful in the synthesis, storage, and secretion of insulin (15). Zn may improve glycemia, and a restored Zn status in patients with type 2 diabetes may counteract the deleterious effects of oxidative stress, helping to prevent complications associated with diabetes (16). A significant negative correlation was found between Zn and glycemic control in this study.

Serum Mn level of diabetic subjects in the current work was significantly different from the value obtained from the control subjects. The percentage of the diabetic subjects with Mn deficiency was however lower than the subjects with Cr and Zn deficiencies. There is evidence that Mn may play a role in the pathogenesis of diabetes (16). Mn has been shown to be important in insulin synthesis and secretion (13). It has been shown that type 2 diabetic subjects responded well to oral doses of Mn (13). Mn is a cofactor of many enzymes including mitochondrial superoxide dismutase (13). Mn-activated enzymes play important roles in the metabolism of carbohydrates, amino acids, and cholesterol (26). There are conflicting reports of Mn deficiency in DM (13,16). Diabetic patients with 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 (13). Diabetic patients with liver disease have been reported to excrete more Mn than those without liver problems (13). High urinary Mn excretion and decreased concentration of hair Mn were observed in diabetic individuals (13,16). It has not been established whether diabetes causes high Mn urinary excretion and low serum level of Mn or whether Mn deficiency contributes to the development of the glucose intolerance (16).

In our study Mg levels were found significantly lower in diabetic patients than in healthy controls. This decrease in serum Mg levels has also been described in earlier studies (4,11,12,14,35,36). The mechanism responsible for hypomagnesemia in patients with DM is not completely known (14). Though serum Mg levels may not accurately reflect the level of total body Mg stores, persistent glycosuria with osmotic diuresis leads to Mg wasting and contributes to high frequency of hypomagnesemia in poorly controlled diabetes (11). The present study demonstrated negative correlation of serum glucose with Mg levels in diabetic patients. Similar associations between serum glucose and serum Mg have been reported by different authors (12,18). An increase in the fasting plasma glucose level associated with the decrease in the fasting plasma Mg level in diabetic patients was earlier demonstrated (12). The serum Mg level has been found to correlate inversely with glycosylated hemoglobin (4,12). These inverse correlations suggest that Zn, Cr, Mn, and Mg nutriture may be found to deteriorate with the abnormal metabolic milieu of diabetes.

In summary, the present study suggests that serum Zn, Cr, Mn, and Mg concentrations were profoundly altered in diabetic patients than in controls. Moreover, the altered Zn, Cr, Mn, and Mg levels were related to the degree of glycemic control.

In this study, an association was established between the serum Pb and diabetes mellitus. There is positive correlation between fasting serum sugar and serum Pb concentrations. Similar positive correlation was also observed by Babalola *et al.* (28). Barbagello *et al.* (37) had reported that as a result of high calcium levels in diabetic patients, the absorption of Pb is expected to be low. But Pb from endogenous sources, such as Pb in the bone and/or from previous environmental exposure, will remain in circulation in the blood. This is probably responsible for the observed high blood level in diabetic patients.

In view of the observed association between serum Pb and DM patients in this study, one may suggest that increased blood Pb in diabetic patients is probably a contributory factor to the decline in renal function observed among diabetic patients. Moreover many other works have linked decline in kidney function to either/both bone or blood Pb levels (28, 38-40). Furthermore, since one of the signs of Pb toxicity is impaired renal function and also one of the most prominent complications of DM is kidney damage, chances are that this observed higher blood Pb in diabetic patients may be associated with the kidney damage complication of diabetes mellitus.

Conclusively, this study revealed that Pb has an interactive connection with type 2 DM. The high serum Pb level in the diabetic patients may also be related to the kidney damage complication associated with the disease. Based on these findings, it is therefore recommended that health-care providers should consider testing diabetic patients for complications due to Pb toxicity as part of the treatment regimen. Also governments should ensure a sweeping ban on the use of leaded gasoline particularly in the third world country.

The experimental work on the measurement of theses trace elements and Pb in urine and hair samples of both groups is in progress. The results will be reported in the future publication.

Traditionally, eating fresh grains, fruit, sea food, and vegetables grown in nutrient-rich soil has been the primary supply for the full spectrum of ionically charged minerals. If agricultural systems fail to provide enough products containing adequate quantities of all nutrients during all seasons, dysfunctional food systems result that cannot support healthy lives and this is the case for many agricultural systems in many developing nations (41).

Unfortunately, naturally occurring, nutrient-rich soil is almost nonexistent on commercial farms. Aggressive farming techniques have stripped most trace minerals from the soil, and the use of nitrogenous fertilizers in agriculture is relatively cheap, and is therefore the foundation of modern farming methods (15,42). Remineralization of the soil, however, is very expensive. When people consume a diet derived from such depleted crops, the intake of essential trace minerals become inadequate, which may lead to poor health and disease (15,28,43). Refining carbohydrate foods also cause a sharp drop in the concentration of various vitamins and minerals (43).

If the serum levels of trace mineral elements (Zn, Cr, Mn, and Mg) for apparently healthy nondiabetic subjects were considered as the normal range for these metals in the study area, the prevalence of these trace mineral element deficiencies in diabetic patients is observed to be 22%-28%. Hence people with diabetes should be encouraged to eat local specific foods rich in Zn, Cr, Mn, and Mg.

CONCLUSION

Type 2 DM is on track to become one of the major global public health challenges of the 21st century. It accounts for approximately 90%–95% of all diagnosed cases of diabetes. Patients with type 2 diabetes may have complications like cardiovascular disease, nephropathy, retinopathy, and polyneuropathy. 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. In the present investigation, the BMI and fasting serum glucose were significantly higher in the diabetic population than in the nondiabetic population of the study. We conclude that the levels of serum Zn, Cr, Mn, and Mg were lower in patients with type 2 diabetes, while serum Pb level was high in the diabetic group than in the nondiabetic control group. This study observed a significant negative correlation between the serum levels of Zn, Cr, Mn, and Mg and the fasting serum levels of glucose in diabetic subjects. A positive correlation was found between concentrations of fasting serum glucose and Pb. The low serum levels of Zn, Cr, Mn, and Mg in diabetic patients than in control subjects may be due to the poor glycemic control. People with diabetes should be encouraged to eat local specific foods rich in these trace minerals. To better understand the role of these trace elements and Pb in diabetes, further clinical studies are required enrolling larger number of patients and using sophisticated techniques besides blood, urine, and hair samples to allow clear conclusions.

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