Zinc, Copper, Chromium, Manganese and Magnesium Levels in Serum and Hair of Insulin-dependent Diabetics

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Abstract

Background: Direct association of trace and macro-elements in relation to human disease has been observed in many research studies. In many cases, an alteration in the metabolism of these minerals has been demonstrated.

Methods: In this investigation, the serum and hair levels of the trace elements zinc (Zn), copper (Cu), chromium (Cr), manganese (Mn) and the macro-element magnesium (Mg) were determined in 40 subjects (20 insulin-dependent diabetics and 20 controls). Samples were analyzed using atomic absorption spectrophotometric methods.

Results: Serum levels for Zn were lower in the patient group in comparison to the controls (p<0.01), however, Zn levels in hair follicles were not found to be statistically different. Serum Cu levels were significantly higher in diabetic subjects (p<0.008) where as hair levels were unaltered. Comparison of levels of Cr in hair samples revealed a significant difference between patients and controls (p<0.001). Serum Mn evaluation revealed no significant difference between mean levels of controls and patients (p<0.06), but hair follicle analysis revealed a significant difference between the two groups. For Mg, statistical analysis indicated a significant difference in the two groups of serum levels (p<0.0007), with hair samples showing no significant difference (p<0.01). These results are consistent with results obtained by some other researchers.

Keywords: Trace elements • diabetes mellitus • zinc • copper • chromium • manganese • magnesium

Introduction

Studies conducted in the 1960s in Shiraz, (Fars province, southern Iran) on the clinical features of nutritional dwarfism (growth retardation and absence of sexual development) and its relation to zinc deficiency were a forerunner for ensuing investigations about the status of certain other trace and macro-elements such as Cu, Cr, Mn and Mg in health and disease in Iran.1 Direct association of trace and macro-elements in relation to human disease has been observed in many research studies. In many cases, an alteration in the metabolism of these minerals has been demonstrated. 2-5

Diabetes mellitus, is a heterogeneous disease characterized by an absolute or relative deficiency of insulin as well as insulin resistance. Numerous authors have evaluated mineral levels and status in diabetic subjects yet, often inconsistent and contradictory results (frequently to the point of non-validity) have been presented.6-8 This difference may be due to the number of subjects, sex and laboratory processing.

Some trace elements act as antioxidants and prevent membrane peroxidation. Others act directly on glucose metabolism. Ceruloplasmin, the major plasma copper transporting protein, possesses a potent antioxidant property. Chromium has been identified as an active component of the glucose tolerance factor (GTF). Manganese is a cofactor for a number of enzymatic systems including arginase which has been found to be elevated in diabetic animals such as rats and mice.9 Magnesium has an important role as a cofactor in the phosphorylation of glucose and in many other enzymatic reactions.
The function of zinc (Zn) in the body metabolism is based on its enzymatic affinity, way of a Zn-enzyme complex or Zn metalloenzyme. In humans and animals, diabetes results in disturbance of this vital trace element.\textsuperscript{10} In most mammals, insulin is stored as Zn crystals and is likely secreted in a Zn form. Zn has an important role in modulating the immune system and its dysfunction in diabetes mellitus may be related in part to the status of Zn.\textsuperscript{11} In diabetics Zn deficiency is associated with a low concentration of Zn in lymphocytes, granulocytes and platelets, low plasma Zn concentration and by a high total body Zn clearance.

In this study we evaluated the levels of Zn, Cu, Cr, Mn and Mg in the serum and hair of Iranian patients with insulin-dependent diabetes mellitus (IDDM) in an effort to evaluate the status of these elements in such patients and to further clarify their role in this disease.

**Materials and Methods**

This study was conducted on a total of 40 Iranian patients from Semnan province, central Iran. The study group consisted of 20 diabetic patients who attended the diabetic clinics and were taking insulin. The control group consisted of 20 healthy volunteers from the university staff with no general complications and receiving no medication. Overnight fasting blood samples were taken, centrifuged and serum was collected and frozen for subsequent analysis.\textsuperscript{12-15}

Hair was cut close to the scalp in the suboccipital area of the head (about 1 to 2 cm) after ascertaining that no coloring agent had been used.\textsuperscript{16} The hair sample was washed twice, first with acetone and then with double distilled water. After heating for 30 min at a temperature of 50-80\degree C, hair samples were digested with 65\% nitric acid and 70\% perchloric acid. Serum and hair samples were analyzed with flame and flameless atomic absorption spectrophotometry (Model AA670 and AA670G, Shimadzu, Japan) respectively. Sample response was compared with standard solution of these inorganic compounds.

**Results**

Mean serum Zn levels in diabetic patients showed a significant decrease as compared to controls (p<0.01); mean value for controls being 145.21 mg/dl (± 30.70) and mean value for patients, 115.83 mg/dl (± 23.64). Mean levels for Zn in hair showed no significant difference between controls and patients (p<0.13); mean levels for controls being 359.15 \( \mu \)g/dl (± 24.31). Cu levels in hair revealed no significant difference (p<0.49) between controls and patients; mean levels for controls: 16.36 \( \mu \)g/g (± 3.89); mean for patients 19.01 \( \mu \)g/g (± 6.31). Analysis of hair samples for levels of Cr found a significant difference between controls and patients (p=0.001). Mean values were 0.3625 \( \mu \)g/g (± 0.23) for controls and 2.418 \( \mu \)g/g (± 2.089) for patients. Analysis of Mn in the serum of controls and patients indicated no significant difference (p=0.96). Mean levels of serum Mn for controls was 1.38 \( \mu \)g/l (± 1.64) and 1.17 \( \mu \)g/l (± 1.30) for patients. Analysis of hair samples for Mn showed significant difference when evaluated using the Mann-Whitney test (p<0.014). Mean value for controls was 0.05 \( \mu \)g/l (± 0.034) and 0.07 \( \mu \)g/l (± 0.028) for patients. Mean values in serum for Mg were 1.72 \( \mu \)g/l (± 0.19) for controls and 1.47 \( \mu \)g/l (± 0.44) for patients. Statistical analysis revealed a significant difference (p<0.0007). Mean values for Mg hair levels showed no significant difference (p<0.01).

**Discussion**

Trace elements are uniquely required for growth and maintenance of life and health. Lack or an inadequate supply of such nutrients produces a functional impairment or can result in disease. The clinical significance and evaluation of trace elements such as Zn, Cu, Cr, Mn and Mg in regard to different diseases including diabetes mellitus remain conflicting as well as controversial and many questions still remain unanswered. Alteration of Zn homeostasis in diabetes is supported by a large body of experimental and clinical evidence. Hagglof\textsuperscript{17} demonstrated that children with newly
discovered IDDM had lower Zn values coupled with high urinary excretion of Zn. Mocchegianai\textsuperscript{11} reported a 20% reduction of plasma Zn levels in IDDM as compared to controls and the same result was obtained by Syogren.\textsuperscript{18} Results of our investigation on Iranian patients were consistent with the above-mentioned studies whereas Zagar\textsuperscript{7}, Melchior\textsuperscript{19} and Martin\textsuperscript{20} showed that the level of Zn in diabetic patients are equal to or higher than that of controls. It has been postulated that low levels of Zn in diabetic patients may be due to excessive urinary output especially in patients with diabetic nephropathy, gastrointestinal malabsorption or genetic factors or signs of infection during which Zn will act as a defense mechanism. High values of this element also may be due to heterogeneity of patients or study design.

The hair follicle is a potentially useful tool for determining the status of zinc and the status of other trace elements and also for assessing any pathological states. The level of Zn in hair for example, is lower in the Zn-deficient population.\textsuperscript{21} However, results obtained with our Iranian patients showed no statistically significant difference in hair Zn levels consistent with the findings of Hagglof.\textsuperscript{17} Many researchers believe that age, sex, pregnancy and seasonal variation may affect the values obtained.

Cu is involved in oxidation-reduction reactions and has a dominant role in diverse proteins such as cytochrome oxidase and cytoplasmic superoxide dismutase. Our results from diabetic patients are consistent with other reports such as Noto\textsuperscript{22} whose study evaluated age as a factor in Cu levels in diabetics and reported higher serum levels of Cu in older subjects. This hypercupremia was also shown by Zagar\textsuperscript{17} and Walker\textsuperscript{6}, especially with diabetic women taking oral contraceptives or with diseases such as retinopathy and hypertension. As it is evident from our observation, the pattern of change in Cu and Zn levels was antagonistic in the serum. The Cu:Zn ratio showed a statistically significant difference (p<0.0005) which was not observed in the hair.

In 1959, Schwartz and Mertz\textsuperscript{23} and later Yoshimoto\textsuperscript{24} and Rabinowitz\textsuperscript{25}, elucidated the action of Cr in diabetes and showed that the administration of Cr may have beneficial effects on the disease. Our patients and Thai\textsuperscript{26} diabetic subjects in a similar study had significantly lower Cr in hair as compared to matched normal subjects. Another study conducted by Aharoni\textsuperscript{27} compared normal pregnant women with pregnant diabetic women and demonstrated higher values of Cr in the diabetic group but a second sampling showed lower values than normal. In general, based on observations from different groups of studies, in addition to impaired Cr utilization, age plays a major role in the status of Cr. Cr levels stabilize at certain ages and then decline.

The important role of Mn in growth and reproduction in rats was shown by Kemmere in 1931.\textsuperscript{28} Later in 1962, Rubenstein\textsuperscript{29} showed that insulin resistant diabetic patients responded well to oral doses of Mn. Appropriate Mn levels are required for development of the normal insulin synthesis and secretion.\textsuperscript{30,31} Unlike Mn values in the hair, serum levels showed no difference between diabetics and controls. Although altered Mn metabolism has been demonstrated as in Walter’s patients\textsuperscript{6}, we found no evidence of change in the Mn status. Their investigation suggested that altered Mn metabolism may be one key in the pathogenesis of diabetes in some cases. More data is needed to be able to verify this point.

Available data from different research studies suggest that hypomagnesemia occurs in a number of diseases including diabetes. Our findings are consistent with others such as Sjogren\textsuperscript{18}, Fujii\textsuperscript{32} and MacNair\textsuperscript{33} who found serum and plasma Mg levels to be lower in diabetic patients than in controls. The mechanism of hypomagnesemia in diabetic patients still remains unsolved but there is enough evidence to suggest that Mg levels drop in the course of recovery from ketoacidosis, during insulin therapy or with severe retinopathy or proteinuria. Mg levels may also decrease due to urinary loss by osmotic action, glucosuria and hyperglycemia. It is possible that hypomagnesemia may be used as an
indicator or marker of the disease. Other reports of normal serum values of Mg and increased concentration of Mg in severe diabetic acidosis have been published.

Even though the data presented in this paper is consistent in some aspects with previous findings of other researchers, the authors feel that additional and more reliable quantitative data must be performed. Larger number of specimens should be obtained in order to fully elucidate the relationship between the trace elements and diabetes mellitus.

References


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