

Correlations of Serum Cu⁺², Zn⁺², Mg⁺² and HbA_{1c} in Type 2 and Type 2 Diabetes Mellitus

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Type 2 Diabetes Mellitus (DM) is one of the most frequently seen. Type 2 DM shows identical pathophysiological features with Type 1 DM but differs in etiology. There are lots of studies in the area of both types of DM which are influencing body by metabolic and oxidative stress. In this study serum Cu, Zn and Mg levels are determined in three patient groups (Type 1 DM, obese Type 2 DM, non-obese Type 2 DM) and discussed the relationships with serum cholesterol, triglycerid, glucose and blood HbA_{1c} levels.

Study groups evaluated as 21 healthy person, 26 non-obese Type 2 DM patients (Body mass index < 25), 28 obese Type 2 DM patients (BMI > 30), 18 Type 1 DM patients

While we didn't find any correlation between parameters of obese Type 2 DM patients, there was slightly negative correlation (r = -0,521, p < 0,05) between Cu and Mg, also the same but positive correlation was found between serum Cu and glucose (r = 0,502, p < 0,05) levels in non-obese Type 2 DM patients. In Type 1 DM group; there was strong negative correlation (r = -0,604, p < 0,05) between serum Cu and Mg levels with a positive strong correlation (r = 0,774, p < 0,001) between serum Cu and blood HbA_{1c} levels. In this group there was also strong negative correlation (r = -0,895, p < 0,001) with serum Mg ve blood HbA_{1c}.

Serum copper levels was increased in all three patients groups, respectively non-obese Type 2 DM, obese Type 2 DM and Type 1 DM group (p < 0,05, p = 0,001, p < 0,001). The meaningful decrease in serum Mg levels (p < 0,05) was only found in Type 2 DM group. There were no significant alterations in levels of serum Zn (p > 0,05).

The results showed that the determination of serum Zn level is not enough to assess the oxidative stress in DM. Because of the probable lacking of serum Zn/Cu antagonism, serum Cu and Mg levels should be determined. In DM, blood HbA_{1c} levels change the profile of trace elements so can be used to assess the degree of oxidative and metabolic stress.

Key words: Type 2 DM, diabetes mellitus, magnezium, Copper, Zinc, HbA_{1c}

Introduction

Diabetes Mellitus is an endocrinological disease having metabolic and oxidative stresses in high

quantity. Type 2 DM shows identical pathophysiological features with Type 1 DM but differs in etiology. Also the nature of both disease complications are generally the same but duration and appearance time are different from each other. Findings show that oxidative stress has the greatest role in developing complications (17-18). Sometimes serum Zn level used to determine the reductant capacity that elevates with Vitamin A, vitamin E (19) and serum Cu level used to determine oxidative stress status which is the cofactor of other

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enzymes in oxidative pathways (20). Level of Zn , an activator of insuline, was investigated in obese patients to corralate with lipogenesis to determine the obesity status (13). The antagonism between Cu and Zn was determined in healthy children of diabetic parent (1). The relationship of trace elements with glycemic regulation is controversial (3). In this study serum Cu, Zn and Mg levels are determined in three patient groups (Type 1 DM, obese Type 2 DM, non-obese Type 2 DM) and discussed the relationships with serum cholesterol, trigliserid, glucose and blood HbA_{1C} levels.

Materials and Methods

Study groups evaluated as group1 healty person, group 2 non-obese Type 2 DM patients (Body mass index<25), group 3 obese Type 2 DM patients (BMI>30), group 4 Type 1 DM patients. Description of groups was shown in Table 1. There were no clinical or laboratory disorder in healthy group. Diseases were excluded in all groups like pancreatitis and anemia by the help of labarotory and clinical findings. Serums were seperated after 30 minutes from collecting blood by santrifuging seperating gel tubes. Then frozen samples were kept at -70°C.

We determined the serum Cu, Zn, Mg levels by Atomic Absorbtion Spectrofotometer Shimadzu model 670/G U-8, blood HbA_{1c} levels with affinity chromographic method by IMx MEIA instrument.

Glucose, cholesterol, trigliserid by enzymatic colorimetric method in otoanalyzer Olympus. Statistical analysis is performed with Paired Samples T test by SPSS 10.0 computer programme

Results

All groups' statistical results is shown in table 2. Correlation analysis was performed on studied parameters between patient groups. There were no significant correlation in obese Type 2 DM group parameters. We found slight correlation in nonobese Type 2 DM group between serum Cu and Mg which was negative (r= -0,521, p<0,05), and between serum Cu and glucose which is positive (r= 502, p<0,05). In Type 1 DM patients there was also slight correlation between serum Cu ve Mg having negative value (r= -0,604, p<0,05), but the correlations between serum Cu and blood HbA_{1C} having positive value (r= 0,774, p<0,001) and between serum Mg and blood HbA_{1C} having negative value (r=-0,895, p<0,001) were significant which is depicted in graphic 1.

Serum Cu levels were increased in nonobese Type 2 DM, obese Type 2 DM and Type 1 DM patients significantly (respectively p<0.05, p=0,001, p<0,001). Serum Mg levels were decreased just only in Tip II DM group (p<0.05) and there were no significant alteration in serum Zn levels.

Table 1.

No	Group	n	Age	Male-female	BMI(Body mass index)
1	Healthy	21	25-57 (49)	12-9	-
2	Non-obese Type II	26	22-68 (55)	13-13	<25
3	Obese Type II DM	28	38-70 (54)	11-17	>30
4	Type I DM	18	14-36 (21)	7-11	-

Table 2.

	Group1 (n=21)	Group2 (n=26)	Group3 (n=28)	Group4 (n=18)
Cu(µg/dL)	88,7+/-23,4	114,9+/-32**	124,6+/-31***	140,8+/-39,8***
Zn(µg/dL)	88,5+/-15,3	89,2+/-18,8	93,3+/-26,6	90,4+/-18,7
Mg (µg/dL)	2,28+/-0,59	2,02+/-0,46**	2,09+/-0,86**	2,1+/-0,23
Cholesterol (mg/dL)	167,7+/-24,7	199+/-46	209+/-27,4	175+/-42
Trigliseride (mg/dL)	116,2+/-82	175+/-107	178,9+/-141	170+/-121
% HbA _{1c}	4,99+/-0,6	7,6+/-2,6	9,1+/-2	9,8+/-2,4

p<0,05 *p<0,001

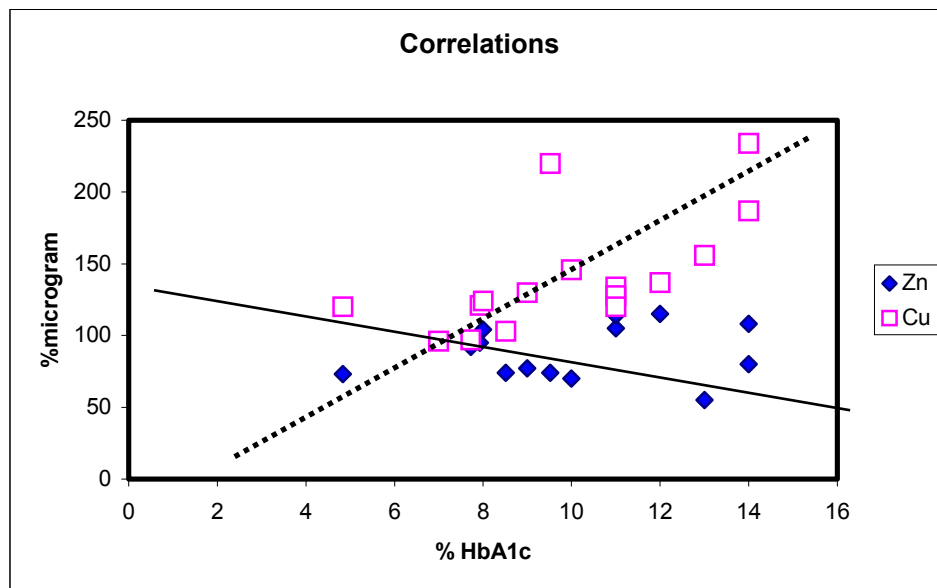


Figure 1.

Zn; $r=0,774$, $p<0,001$ Mg; $r=-0,895$, $p<0,001$

Discussion

Oxidative damage due to free radicals is associated with vascular disease in people with Type 1 and those with Type 2 diabetes mellitus (22). There are several potential sources of increased free radical production in diabetes including autooxidation of plasma glucose and increased transition metal bioavailability (24). The radical – scavenging antioxidant activity of the serum of people with either Type 1 or 2 DM is lower than that of age-matched controls. This may be attributed with the trace elements (24). On the trace elements increase in the Cu ion levels in patients with DM might be attributed to hyperglycemia that may stimulate glycation and release of copper ions and this accelerate the oxidative stress so AGEs formation is occurred (25). Also we know that in people with type 1 DM receiving Zn supplementation improve in antioxidant status (26). The potential antioxidant effects of Zn in diabetes (27) could be related to several mechanism. It has been suggested that Zn metallothionein complexes in the islet cells provide protection against immune-mediated free-radical attack. Zinc could also in protecting sulfhydryl groups against oxidation and participate in the inhibition of the free radical in Haber Weiss cycle by competing with transition metals. The objective of this study was to determine the effects of Zn and Cu and Mg on oxidative stress in people with diabetes mellitus.

In the patients with diabetes mellitus, contradictory findings about profile of serum trace elements were found (4). But a general consensus exists about the increased level of copper, the most important co-factor of oxidative and reductive reactions (6, 8, and 12). This finding that is compatible with our finding indicates that copper increases with the oxidative stress. A difference between groups on the level of this increase seems present. The fact that increase in the serum copper level in the obese patients with diabetes mellitus Type 2 is more prominent than in non-obese patients is important to show the load of obesity stress on the body. The fact that the patients with diabetes mellitus Type 1 have the highest serum copper levels and a body-mass index (BMI) lower than 30 percent makes it imperative to search the effects of insulin on trace elements since the relation between copper and insulin-bound zinc is controversial (20). Because the Zn element in insulin may differs the Cu metabolism. But in this case this regulation were absent and serum Cu levels were in expected values in oxidative conditions. So additional insulin effect need to further studies. Homologous insulin applied to these patients whose autonomous insulin production is absent, seems failed to prevent oxidative stress. This is compatible with the fact that complications in this group occur in earlier ages.

In group IV, strong positive correlation between copper and HbA_{1c} that represents blood glucose regulation supplies our findings. The relation between HbA_{1c}, which shows the glucose regulation, and the increasing copper value supports our view that Cu is an important marker for oxidative stress. Because HbA_{1c} levels rise with the poor control of diabetes mellitus. Although the correlations between serum copper and HbA_{1c} levels determined in the studies of Ruiz C. and some other authors were not found to be meaningful, but there is a very nearly consensus about the antagonism in the levels of HbA_{1c} and Zn in diabetes mellitus (6,15). Quillio et al advocated that hyperglycemia, by increasing zinc excretion contributes this correlation. Considering the circadian variations of serum zinc levels and the fact that role of zinc in oxidative-reductive reactions has not been understood precisely, use of blood HbA_{1c} levels for this purpose seems much more suitable than Zn or Cu levels in diabetes mellitus.

Regarding to serum zinc levels, there were no meaningful (significant) difference between groups. There are some investigators who found decrease in serum Zn levels as well as the other investigators like D'Ocon found that serum Zn levels increased in diabetes mellitus (3, 7, 14). Although some investigators suggest that decreased serum zinc levels can be prevented by oral zinc replacements, later search indicated that different representations of serum zinc level are independent from diet (2, 7, 12). Considering all of the findings together, it is supplied that the ratio of serum Cu/Zn levels, instead of serum zinc levels alone provides more useful information (4, 15) because as we found in our study, the antagonism in the levels Cu and Zn that exist in physiologic conditions may disappear so the role of insulin becomes more important in trace elements in diabetes mellitus.(1, 13, 14).

We found slightly correlation in nonobese Type 2 DM group between serum Cu and Mg which was negative. In Type 1 DM patients there was also slight correlation between serum Cu ve Mg having negative value, and serum Mg and blood HbA_{1c} having negative value. The fact that serum magnesium levels is decreased in the patients with diabetes mellitus Type 1 and Type II. There were a correlation between serum magnesium levels and other parameters but this correlation not always be exist, and this indicates that Mg element can be regulated by more sophisticated and complex

mechanisms. And this situation dictates more detailed studies to be performed.

In our study plasma triglyceride and cholesterol levels were moderately elevated. Regarding to lipid levels, there were not significant difference between groups. However, the hyperlipidemia in diabetes mellitus is often characterized by an increase in the small, dense LDLs (28), which are particularly atherogenic; this increase occurs even in the absence of hyperlipidemia (28) In addition, a portion of the plasma LDL undergoes glycosylation, which may increase susceptibility to oxidative stress.

Finally, it has been found that serum zinc level alone doesn't suffice to evaluate oxidative stress in the patients with diabetes mellitus, the antagonism between Zn and Cu doesn't always validate and consequently, other trace elements such as copper and magnesium should also be determined. Furthermore, it has been understood that HbA_{1c} levels in the patients with diabetes mellitus contributes to the changes in the profile of blood trace elements and as a result of this, contributes to the degree of oxidative stress. So it has been suggested that blood HbA_{1c} levels may be used for this purpose.

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