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Serum trace elements in obese women with or without diabetes

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***Background & objectives*: Relationship of trace elements with obesity and diabetes is complex, alterations in their metabolism can be induced by the diseases and their complications. To study the role of the trace elements in diabetes and obesity, serum trace elements levels (Cr, Se, Fe, Zn, Cu and Mn) were measured in obese women with or without diabetes as well as healthy women. Further, correlation between serum trace elements levels and glucose, insulin, homeostasis model assessment (HOMA-IR), glycated haemoglobin (HbA_1c), body mass index (BMI), waist circumferences, waist -to -hip ratio and high-sensitivity C-reactive protein (hsCRP) were also determined in these women.**

***Methods*: This study was performed with morbidly obese (BMI >40 kg/m^2) women with diabetes (n=41), without diabetes (n=45) and 50 healthly non obese women. Anthropometric measurements were taken and levels of serum Zn, Cr, Fe Cu and Mn were determined. Biochemical parameters included serum glucose, insulin, lipids, haemoglobin, hsCRP and HbA1C.**

***Results*: The levels of Zn (P<0.001), Mn (P<0.05), Fe (P<0.05) were significantly lower and the level of Cu (P<0.001) and Cu / Zn ratio (P<0.05) were significantly higher in the diabetic obese women than those of the healthy women. Also, the levels of Zn and Fe were significantly lower and the levels of Cu were significantly higher in the non diabetic obese women than those of the healthy group. Serum Zn levels negatively and serum Cu levels positively correlated with anthropometric values in diabetic and non diabetic obese women. Further, serum Zn, Mn and Cr levels negatively correlated and serum Se levels positively correlated glycaemia control parameters in diabetic obese women. In addition, serum Zn levels negatively correlated with hsCRP in diabetic and nondiabetic obese females.**

***Interpretation & conclusions*: Our findings showed significant association between Zn and Fe deficiencies and obesity. Also, obese women with diabetes may be at a greater risk of developing imbalances and deficiencies of trace elements compared with obese women without diabetes.**

Key words Chromium - diabetes - iron - obesity - selenium - trace element - zinc

Obesity is a worldwide disease affecting population of all age groups and socio-economic levels, in both developed and developing countries. It is known to be a contributory risk factor for several disease states, including diabetes mellitus[1,2]. Trace elements are essential nutrients with regulatory, immunologic, and antioxidant functions resulting from their action as essential components or cofactors of enzymes

throughout metabolism[3]. Trace elements and minerals influence the pathogenesis of obesity and diabetes and their complications, mainly through their involvement in peroxidation and inflammation[4].

In obese people the metabolic disturbances are decompensated. Although, overweight is a preclinical condition, obesity is the clinically manifested metabolic disorder, including mineral imbalances[5]. Women seemed to be more at risk for toxic metal exposure than men and at the same time more vulnerable to micronutrient deficiency[6]. The clinical significance and evaluation of trace elements in different diseases including remain controversial and many questions still remain unanswered. Therefore, the aim of the present study was to compare serum trace elements levels [chromium (Cr), selenium (Se), iron (Fe), zinc (Zn), copper (Cu) and manganese (Mn)] in morbidly obese (BMI greater than 40 kg/m^2) women with or without diabetes, and healthy females. The correlations between serum trace elements levels and body mass index (BMI), waist circumferences, waist-to-hip ratio, glucose, insulin, homeostasis model assessment of IR (HOMA-IR) and HbA1c were also examined in these women. The acute-phase response to injury or infection is known to be associated with alteration in dynamics of many trace elements[7]. The change varies directly with the degree of the acute phase response which can be judged by the concentration of C-reactive protein. Therefore, the correlation between serum trace elements levels and high-sensitivity C-reactive protein (hsCRP) was also examined in these women.

Material & Methods

Study population: This study was performed in Konya Turkey between May and October 2011, on 45 non diabetic obese women aged 20-60 yr (mean 37.9 ± 12.0 yr), 41 obese women with diabetes aged 20-60 yr (mean 43.9 ± 10.0 yr) and 50 healthy women aged 20-60 yr (mean 40.64 ± 10.2 yr). All consecutive female patients diagnosed with type 2 diabetes mellitus and obesity in Cardiology Clinics of Meram Medical School, Konya, Turkey, were recruited into the study. The control group consisted of women selected from hospital personnel known to be healthy. BMI was used as an obesity criteria[8]. The categories were defined as: morbidly obese women - BMI >40 kg/m^2 and healthy women – BMI 18.5 to -25 kg/m^2. Exclusion criteria were severe chronic diabetic complications (proliferative retinopathy, albuminuria, symptomatic neuropathy), malignant diseases, chronic liver disease, hypertension, a history of cardiovascular disease, infectious disease, pregnancy, alcohol and smoking habit and taking a supplement vitamin, mineral, antioxidant, fish-oil tablet. The study protocol was approved by the Ethics Committee of Meram Medical School, University of Selcuk, Turkey. All patients were informed of the details of the study and the written consent of each patient was received.

Anthropometric measurements: All anthropometric measurements were made with participants wearing light clothing and no shoes. BMI was measured in all participants and calculated as weight (in kilograms) divided by height (in meters) squared, and participants waists were measured with a soft tape midway between the lowest rib and the iliac crest. The hip circumferences was measured at the widest part of the gluteal region.

Biochemical analysis: Blood samples (5 ml) were obtained after an overnight fasting in clean and minerals free tubes. Serum samples were obtained after centrifugation and samples were stored frozen at -80 ^{o}C until the day of analysis. Serum lipids, haemoglobin, hsCRP, glucose, HbA1c and insulin levels were measured immediately.

Analyses of trace elements: Serum Zn and Cu levels were determined using atomic absorption spectrophotometer (Rayleigh WFX-320, China, Mainland). The slit width was 0.4 nm, lamp flow was 3.0 mA, wavelegth were 213.9 and 324.7 nm respectively. The levels of serum Zn and Cu were calculated after application of absorbances on suitable calibration curve for each element made from standard solutions. Serum samples were diluted 5-fold with 1 per cent nitric acid (Merck, Darmstadt, Germany) immediately before the assay. All of the reagents were of analytical grade and water was double distilled.

An Agilent 7500 Ce inductively coupled plasma mass spectrometry (ICP-MS) system (Tokyo, Japan) was used for the measurements of the levels of trace elements (Se, Mn, Cr) in serum and using an multi-element standard solution for 4 and inductively coupled plasma (ICP) (Sigma-Aldrich, USA). The instrument operating parameters are presented below: integration time: 0.6 sec; RF power (W): 1550; plasma gas flow rate (l/min): 15; auxiliary gas flow rate (l/min): 0.90; carier gas flow rate (l/min): 0.93; sampling depth (mm): 7.1; acqusition mode: spectrum; mumber replicates: 3, cone: octapole. Serum Fe levels were measured by commertially available kits based on routine methods on the Synchron LX System (Beckman Coulter, USA).

Analyses of other analytes: Serum total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-cholesterol), low density lipoprotein cholesterol (LDL-cholesterol), glucose, haemoglobin and hsCRP levels were measured by commercially available kits based on routine methods on the Synchron LX System (Beckman Coulter, Fullerton CA, USA). Serum insulin was determined by routine chemiluminescence method on E170 analyzer (Roche Diagnostics, Mannheim, Germany). HbA1c levels were determined by using the ready-to-use reagent kit on Automated Glycohemoglobin Analyzer HLC-723G8 (Tosoh; Japan). HOMA-IR was calculated as insulin (milliunits per liter) × glucose (millimoles per liter)/22.5[9].

Statistical analysis: All data are expressed as mean ± standart deviations (SD). Statistical analysis were done using SPSS v. 16.0 (SPSS Inc., IL, USA). The normality of the variables was evaluated using the one-sample Kolmogorov-Smirnov test. The normal distribution of variables were examined with one-way ANOVA; tukey test, and non-normally distributed variables were examined by Kruskal-Wallis H test. The correlations between variables were performed by Pearson's Correlation test. A post-hoc power analysis was conducted to determine the effect of the changes in study size for each analysis. Differences were considered significant at a probability level of $P<0.05$.

Results

Clinical characteristics and biochemical parameters of the study subjects are presented in Table I. BMI, waist circumference, waist-to-hip ratio, fasting blood glucose, fasting blood insülin, HbA_1c, HOMA-IR, total cholesterol, triglycerides, hsCRP, Cu levels and Cu/Zn ratio of the diabetic obese females were significantly higher ($P<0.001$ for Cu/Zn ratio and $P<0.05$ for the other parameteres), whereas HDL-cholesterol, Zn, Mn, Cr and Fe levels were lower than those of the healthy females ($P<0.05$ for Mn and Cr and Fe $P<0.01$ for HDL-cholesterol, and $P<0.001$ for Zn). In addition, BMI, waist circumference, waist-to-hip ratio, fasting blood insülin, HOMA-IR, triglycerides, hsCRP and Cu levels of the non diabetic obese females were significantly higher ($P<0.01$ for triglycerides and $P<0.001$ for the other parameteres) whereas HDL-cholesterol, Zn and Fe levels were lower than those of the healthy females ($P<0.05$ for Mn and $P<0.001$ for the other parameteres). Further, fasting blood glucose, HbA_1c levels and HOMA-IR values were significantly higher in the diabetic obese females than those of the non diabetic obese females ($P<0.001$). Fasting blood insülin, total cholesterol and triglycerides levels were significantly lower in the non diabetic obese females than those of the diabetic obese females ($P<0.05$ for fasting blood insülin, $P<0.01$ for total cholesterol and $P<0.001$ for triglycerides). In addition, no significant differences were observed in systolic and diastolic blood pressure, LDL-cholesterol and haemoglobin levels.

Simple correlation analyses were performed to investigate the association of serum trace elements levels with BMI, waist circumference and waist- to- hip ratio. The levels of Cu were positively correlated with BMI and waist circumference in diabetic obese women ($P<0.05$). On the other hand, the levels of Zn were negatively correlated with BMI ($P<0.01$) and waist circumference ($P<0.05$) in non diabetic obese women. The levels of Cu were positively correlated with BMI and waist circumference in non diabetic obese women ($P<0.05$) (Table II).

The serum Zn levels negatively correlated with glucose levels ($P<0.05$) and HOMA-IR values ($P<0.01$) in diabetic obese women and negatively correlated with HbA1c levels and HOMA-IR ($P<0.05$) values in non diabetic obese group. The serum Se levels positively correlated with glucose and HbA_1c ($P<0.05$) levels in diabetic obese and positively correlated with HOMA-IR values ($P<0.05$) in non diabetic obese subjects. The serum Mn levels negatively correlated with insulin ($P<0.05$) in diabetic obese group. The serum Cr levels negatively correlated with serum glucose and HbA_1c levels ($P<0.05$) in diabetic obese women (Table III). The serum Zn levels negatively correlated with hsCRP levels in diabetic ($P<0.01$) and non diabetic obese women ($P<0.05$) (Table IV). Post-hoc power analysis revealed observed power ($1-\beta = 0.88$) for Zn, ($1-\beta = 0.97$) for Cu, ($1-\beta = 0.61$) for Mn, ($1-\beta = 0.73$) for Cr and ($1-\beta = 0.62$) for Fe.

Discussion

Zn status, particularly circulating level, is known to be altered in conditions such as obesity and type 2 diabetes[10]. Obese people experience chronic inflammation resembling that found in infections[11]. Studies showed that Zn deficiency increases the concentration of inflammatory cytokines[12]. In our study, serum Zn levels were significantly lower and serum hsCRP levels, which are controlled by cytokines, were significantly higher in the diabetic and non diabetic obese women than those of healthy females. In addition, serum hsCRP levels were negatively correlated with Zn

Table I. Clinical characteristics and biochemical variables of the diabetic obese, nondiabetic obese and healthy females

	Control subjects (n=50)	Non diabetic obese subjects (n=45)	Diabetic obese subjects (n=41)	Mean comparison *(P)*
Age (yr)	41.37 ± 8.3	39.83 ± 12.2	43.90 ± 9.9	0.216
Diabetes duration (yr)	-	-	6.28 ± 4.3	-
BMI (kg/m^2)	22.14 ± 2.0	43.48 ± 6.5*	41.63 ± 7.3*	<0.001
Waist circumference (cm)	78.50 ± 5.7	119.27 ± 11.7*	118.18 ± 11.5*	<0.001
Waist-to-hip ratio	0.79 ± 0.04	0.86 ± 0.08*	0.86 ± 0.06*	<0.001
Systolic blood pressure (mmHg)	123.50 ± 1.1	129.52 ± 3.7	133.14 ± 5.6	0.084
Diastolic blood pressure (mmHg)	85.25 ± 1.6	89.31 ± 1.7	92.61 ± 2.0	0.062
Fasting blood glucose (mg/dl)	84.10 ± 7.4	92.31 ± 7.7	185.09 ± 87.8$^{*,\#}$	<0.001
Fasting blood insülin (µU/ml)	5.74 ± 2.7	16.79 ± 17.8$^{*,+++}$	24.49 ± 19.1*	0.001
HbA1c (%)	5.32 ± 0.3	5.48 ± 0.4	8.30 ± 3.2$^{*,\#}$	<0.001
HOMA-IR	1.18 ± 0.6	3.40 ± 2.0*	7.70 ± 4.8$^{*,\#}$	<0.001
HDL cholesterol (mmol/l)	1.37 ± 0.3	1.11 ± 0.3*	1.17 ± 0.2**	<0.001
LDL cholesterol (mmol/l)	2.88 ± 0.8	3.17 ± 0.9	3.26 ± 0.8	0.144
Total cholesterol (mmol/l)	4.63 ± 0.9	4.96 ± 1.0^{+}	5.65 ± 1.0*	0.001
Triglycerides (mmol/l)	0.80 ± 0.4	1.41 ± 0.6$^{**,++}$	2.79 ± 1.4*	<0.001
Haemoglobin (g/dl)	12.88 ± 2.1	11.77 ± 2.3	12.06 ± 2.2	0.055
hsCRP (mg/l)	4.55 ± 2.7	13.15 ± 7.1*	15.16 ± 9.2*	<0.001
Zinc (Zn) µmol/l	15.34 ± 2.7	12.89 ± 3.5**	11.60 ± 3.2*	<0.001
Copper (Cu) µg/dl	113.04 ± 31.3	150.65 ± 34.4*	158.92 ± 36.9*	<0.001
Selenium (Se) µg/l	132.94 ± 13.8	134.85 ± 18.9	137.88 ± 22.6	0.434
Manganese (Mn) µg/l	0.29 ± 0.2	0.26 ± 0.1	0.20 ± 0.09***	0.044
Chromium (Cr) µg/l	2.53 ± 1.6	2.36 ± 0.9	1.86 ± 0.6***	0.018
Iron (Fe) µg/dl	57.70 ± 34.1	41.33 ± 24.6***	39.64 ± 20.5***	0.028
Cu / Zn	6.75 ± 3.5	8.04 ± 7.2	10.17 ± 6.3***	0.023
Cu / Fe	2.48 ± 4.2	3.44 ± 3.6	4.37 ± 2.2	0.261

All values are mean ± standart deviations. One-way ANOVA for means comparison

BMI, body mass index; HbA1c, glycated haemoglobin; HOMA-IR, homeostasis model assesment; HDL, cholesterol, high density lipoprotein-cholesterol; LDL, cholesterol, low density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; P^{*}<0.05, **<0.01, ***<0.001 compared with control group; P^{+}<0.05, $^{++}$<0.01, $^{+++}$<0.001 compared with diabetic obese group; $^{\#}P$<0.001, compared with nondiabetic obese group

Table II. Correlations of serum trace elements levels with clinical variables of the diabetic obese, nondiabetic obese and healthy women

	Control subjects (n=50)			Non diabetic obese subjects (n=45)			Diabetic obese subjects (n=41)		
	BMI	Waist circumference	Waist-to-hip ratio	BMI	Waist circumference	Waist-to-hip ratio	BMI	Waist circumference	Waist-to-hip ratio
Zn	0.110	-0.141	-0.191	-0.529**	-0.343*	-0.022	-0.121*	-0.148	-0.238
Cu	-0.230	-0.029	0.094	0.374*	0.395*	0.091	0.549*	0.625*	0.197
Se	0.147	-0.136	-0.015	-0.044	-0.338	-0.165	0.150	0.160	0.159
Mn	0.117	-0.045	-0.036	-0.298	-0.197	0.120	0.102	0.026	-0.049
Cr	-0.135	-0.016	-0.022	-0.015	-0.211	0.109	0.118	0.101	0.002
Fe	-0.063	-0.137	-0.018	0.284	0.235	-0.116	0.010	0.037	0.045

BMI, body mass index; $^{*}P$< 0.05; $^{**}P$<0.01

Table III. Correlations of serum trace elements levels with biochemical variables of the diabetic obese, nondiabetic obese and healthy females.

	Control subjects (n=50)				Nondiabetic obese subjects (n=45)				Diabetic obese subjects (n=41)			
	Glucose	Insulin	HbA1c	HOMA-IR	Glucose	Insulin	HbA1c	HOMA-IR	Glucose	Insulin	HbA1c	HOMA-IR
Zn	-0.032	-0.089	0.144	0.083	0.157	-0.246	-0.427*	-0.107*	-0.364*	-0.161	-0.201	-0.597**
Cu	-0.017	0.185	0.088	0.272	-0.225	-0.319	0.106	-0.142	0.141	0.065	0.048	0.041
Se	0.068	0.138	-0.015	-0.236	0.212	0.209	0.314	0.348*	0.376*	0.063	0.378*	0.180
Mn	-0.002	-0.169	0.079	-0.091	-0.069	-0.287	-0.157	-0.288	-0.019	-0.354*	-0.290	-0.223
Cr	-0.019	0.134	-0.051	-0.011	0.156	-0.318	0.028	-0.013	-0.356*	-0.033	-0.380*	-0.058
Fe	0.109	-0.287	-0.184	-0.222	-0.128	-0.196	-0.254	-0.139	-0.256	-0.166	-0.299	-0.144

HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assesment; *$P< 0.05$; **$P< 0.01$.

levels in the diabetic and non diabetic obese women. It appears that serum concentration of Zn is modified by the presence of a systemic inflammatory response.

In trace element metabolism the best known interaction is the reported antagonism between zinc and copper[13]. The present study demonstrated that serum Cu levels in the diabetic and non diabetic obese women were significantly higher than those in healthy control group. Earlier studies on obese subjects found that serum Cu levels were significantly higher in obese group than controls subjects[2,14]. Higher serum Cu levels were also shown by other investigators[15-17].

In our study, association of trace elements with glycaemia control parameters especially HOMA-IR values was assessed. HOMA-IR is a convenient and beneficial method for evaluating insulin resistance, especially in obese subjects, and reflects insulin resistance obtained by euglycaemic clamp more accurately than fasting plasma insulin levels alone[9]. Negative correlations were found between serum Zn levels and HbA1c and HOMA-IR in the non diabetic obese women, and also between serum Zn levels and HOMA-IR in the diabetic obese women. Previous studies have shown that serum Zn levels are lower in diabetic patients than those of non diabetic subjects, increased urinary Zn excretion being the main reason[18]. Zn is essential for insulin synthesis and release, and its deficiency seems to impair release of insulin[3]. Zn could have direct insulin-like effects, which may be due to inhibition of the important glycogen-regulating enzyme GSK3. Other mechanisms include stimulation of the post-receptor proteins Akt and phosphatidylinositol 3-kinases. Zn may also reduce cytokines such as Interleukin-1β as well as nuclear factor kappa-light-chain-enhancer of activated B cells[19].

Table IV. Correlations of serum trace elements levels with serum hsCRP levels of the diabetic obese, non diabetic obese and healthy females

	Control subjects (n=50)	Non diabetic obese subjects (n=45)	Diabetic obese subjects (n=41)
	hsCRP	hsCRP	hsCRP
Zn	-0.089	-0.414*	-0.495**
Cu	0.061	0.387	0.294
Se	-0.123	-0.159	-0.100
Mn	-0.049	-0.155	0.214
Cr	-0.161	0.163	-0.130
Fe	0.259	-0.097	-0.049

hsCRP; high-sensitivity C-reactive protein; *$P<0.05$; **$P<0.01$

In the present study no significant differences were found between serum Se levels of the groups. However, serum Se levels were positively correlated with serum glucose and HbA_1c levels in the diabetic obese group and positively correlated with HOMA-IR values in the non diabetic obese women. Laclaustra *et al*[20] have found that high serum Se concentrations were associated with a higher prevalence of diabetes, as well as with higher fasting plasma glucose and HbA_1c levels. Stranges *et al*[21] have reported a significant positive association between plasma Se and glucose levels at both baseline and follow up. Se functions as a part of proteins known as selenoproteins. Through these selenoproteins, Se may play roles as a defensive mechanism for oxidative stress, for the regulation of thyroid hormone activity, and for the redox status of vitamin C and other molecules[22]. However, it is known that the therapeutic window of Se is narrow, and adverse health effects may occur due to supranutritional Se intake even below the levels

required for intoxication[23]. High-Se diets may stimulate the release of glucagon, promoting hyperglycaemia, or may induce overexpression of glutathione peroxidase-1 and other antioxidant selenoproteins resulting in insulin resistance and obesity[21].

Manganese acts as a catalyst in the breakdown of fats and cholesterol. It is essentially required for the metabolism of vitamin B_1, C and E, and for activation of various enzymes which are important for proper digestion and utilization of foods[24]. In our study, serum levels of Mn were significantly lower in diabetic obese women than those of healthy group. Also, serum Mn levels were negatively correlated with serum insulin levels in the obese diabetic women. It has been reported that people with diabetes may often have a serious Mn deficiency[25]. Appropriate Mn levels are required for development of the normal insulin synthesis and secretion[26]. People with diabetes have been shown to have significantly lower levels of Mn in serum than that in healthy people[27,28].

Our results indicated no association between serum Cr levels and obesity. It has been demonstrated that chromium supplementation reduces body weight, regulates hunger, and also decreases body fat[30,31]. Such difference may be due to race, lifestyle, geographical influence and even analytical methods. Our findings showed an association between serum Cr levels and diabetes. Dietary deficiency of Cr is belived to be positively associated with the risk of diabetes and its complications[32]. Chronic treatment with a Cr complex of D-phenylalanine improved glucose tolerance and insulin resistance in an obese mouse model of type 2 diabetes[29]. Kazi *et al*[28] reported that Cr levels were significantly reduced in diabetic patients.

In our study, significantly decreased serum Fe levels in both diabetic and non diabetic obese women than those of the healthy group were in agreement with the findings of many other investigations[13,33].

In conclusion, our findings showed associations between Zn and Fe deficiencies and obesity. Also, there were negative associations between serum Cr and Mn levels and diabetes. The obese women with diabetes may be at a greater risk of developing imbalances and deficiencies of trace elements compared to obese non diabetic women. Further, studies with a large sample need to be done to elucidate the relationship between these trace elements and obesity and diabetes.

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