Do copper and zinc levels predict metabolic syndrome and metabolic syndrome's parameters as hs-CRP does?

Bakır ve çinko düzeyleri metabolik sendromu ve metabolik sendrom parametrelerini hs-CRP gibi öngörebilir mi?

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Abstract
Being a significant factor indicative of inflammation, hıgh sensitive C reactive protein (hs-CRP) is also predictive for atherosclerosis. It is acknowledged that the efficacy of antioxidant defense mechanism is reduced by the changes in trace element levels. These changes also increase the negative effects of free oxygen radicals on cell integrity. It is known that hs-CRP is a marker in predicting metabolic syndrome (MS) and its parameters. In this study we aim to find some other markers and compare the relation of Cu and Zn levels with MS and MS parameters.410 patients (90 men and 320 women) were included in this study. The measurement of waist and hip circumferences are performed. Fasting plasma glucose, postprandial plasma glucose, insulin, copper, zinc, lipid profile, hsCRP levels were examined. All the analyses were done according to diagnosis criteria of NCEP-ATP III. BMI, HDL and Cu levels were significantly higher in women when compared to men ($P < 0.001$). As hsCRP does, blood copper levels were found to predict MS and MS parameters. However, it is different from each other in that copper levels predicted different MS parameters at different sensitivity and specificity. We also observed that there was a more significant correlation between TG level, blood pressure and Cu, compared to hsCRP. When all these results are taken into consideration, Cu can be thought as an alternatıve marker in predicting MS and MS parameters. Being influenced less than CRP by the inflammatory events, Cu is a beter predictor for MS and atherosclerosis.
Keywords: Metabolic Syndrome, hs-CRP, Zinc, Copper, Inflammatory Marker

Özet
Yüksek duyarlıklı C- reaktif protein (YD-CRP) ateroskleroz gelişimini belirleyen inflamatuar süreç için önemli bir yol gösterici olarak kabul edilmektedir. Eser elementlerin düzeylerindeki azalmaların antioksidan seviyelerini azalttığı ve hücre bütünlüğüne negatif etkisi olduğu bilinmektedir. Metabolik sendrom ve metabolik sendrom bileşenlerinin gelişiminde eser elementlerden olan bakır ve çinkonun da YD-CRP gibi yol gösterici olarak kullanılabileceği bu çalışmanın ana amacıdır. Çalışmaya 410 hasta dahil edilmiştir (320 kadın, 90 erkek). Hastaların bel ve kalça çevreleri ölçülmüştür. Açlık kan şekeri, tokluk kan şekeri, insülin düzeyleri, bakır ve çinko düzeyleri, lipid profilleri ve YD-CRP düzeyleri incelenmiştir. NCEP-ATP III kriterlerine göre hastalar metabolik sendrom tanısı almıştır. Vücut kitle indeksi, yüksek yoğunluklu lipoprotein Düzeyi ve Bakır kan seviyeleri kadınlarda erkeklere göre yüksek bulunmuştur ($P < 0.001$). Kan bakır düzeylerinin MS ve MS parametrelerini öngörmede YD-CRP kadar etkili olduğu saptandı. Ayrıca trigliserit, bakır düzeylerinin ve kan basıncının YD-CRP ile daha korele olduğu görüldü. Kan bakır düzeyi MS sendrom gelişim sürecinde YD-CRP gibi bir takip parametresi olarak kullanılabilir. YDCRP'nin inflamatuar süreçten bakıra göre daha fazla etkilenmesi bakır seviyesi ölçümünü MS gelişim sürecini öngörmede YD-CRP'den daha değerli kılabilir.
Anahtar kelimeler: Metabolik sendrom, YD-CRP, Bakır, Çinko, İnflamatuar belirteç

Introduction

Atherosclerosis known as complication of metabolic syndrome and it is the most important health problem in the world, leading mortality and morbidity. It has increased dramatically and many studies carried out to find out a marker that can help predict MS and its complications. High sensitivity C-reactive protein (hs-CRP) has been regarded as quite a valuable marker to predict MS and atherosclerosis (1). It has been suggested that oxidative stress is related to MS and atherosclerosis, and may also contribute to pathogenesis of insulin resistance (2). It is know that the changes in trace element levels reduce the efficacy of antioxidant defense mechanism and increase the negative effects of free oxygen radicals on cell integrity (3). Of all the endogenous

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Received: 01.04.2015 **Accepted:** 21.05.2015
www.gaziantepmedicaljournal.com
DOI: 10.5455/GMJ-30-183002

antioxidants superoxide dismutase (SOD) is the most important and it changes superoxide radical into H2O2 and O2 (4-5). Zinc (Zn) is the cofactor of SOD. One of the other component of SOD is Copper (Cu). Thus, copper and zinc contribute to antioxidant system (4-6). Copper is also the cofactor of SOD and catalyzed the generation of reactive oxygen products and membrane lipid peroxidation. Zinc is an important element which protects the immune system and it has also an important role in DNA and protein synthesis (7). In the view of such information we thought that the trace elements Cu and Zn may be related to oxidative stress and consequently to MS components.Thinking that it may be some other markers, alternative to CRP in predicting MS parameters and atherosclerosis, we aim to compare the relation of Cu and Zn with Ms and its parameters.

Materials and Methods

This study enrolled 410 patients (90 men and 320 women) who visited the internal medicine out-patient clinic of Ankara Training and Research Hospital. Those that have the symptoms (hernia, acid, intra-abdominal mass or pregnancy etc.) affecting the accuracy of waist circumference measurements , those that have orthopedic abnormalities affecting anthropological measurements and those that have acute diseases for any reason are excluded from the study.

Patients included in this study were questioned for the presence of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, family history, smoking, and drug usage.

Following physical examination, their waist and hip circumferences were measured according to techniques suggested by the International Biological Program (IBP) and Anthropometric Standardization Reference Manual (ASRM). Blood pressure measurement (BPM) was taken from the right arm with a mercury manometer in the sitting position after at least a 5 minute rest. Waist circumference was measured at a level midway between the lower rib margin and iliac crest while the body is in horizontal position.Hip circumference was measured at the maximum width over the buttocks. For height and weight measurements patients were asked to take off their shoes and heavy outer garments. Body Mass Index (BMI) was calculated by dividing weight expressed in kilograms into the square of height expressed in meters (kg/m2). Fasting plasma glucose, postprandial plasma glucose, insulin, copper, zinc, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride and hs-CRP levels of all the patients were examined. Blood samples were taken between 9-11 a.m. after at least 12 hours of fasting. Glucose, total cholesterol and HDL cholesterol were measured in the biochemistry laboratory; original Roche Diagnostics kits were measured on the Triglyceride Roche Modular DP analyser. LDL Cholesterol were calculated with Friedewald formula. Measurements of serum Cu and Zn were performed by spectrophotometric method disorder; along with those who-had low HDL cholesterol and excessed the limit of high triglyceride, the ones who used drugs for dyslipidemia were diagnosed with both HDL cholesterol and triglyceride. The homeostasis model assessment of insulin resistance (HOMA-IR) was applied evaluate insulin sensitivity. HOMA values of all patients were calculated by the following formula: "[Fasting blood insulin (μU/ml) x fasting blood glucose (mg/dL)] Thinking that increase in hs-CRP levels might occur secondary to inflammation, the patients whose hs-CRP levels were 10mg/L and above 10mg/L weren't evaluated.

Statistical analysis

Statistical analysis of data was performed using SPSS for Windows 11.5 Package program. Student's t Test was used to compare quantitative data chi-square test was used to compare categorical data. Logistic regression analysis was performed to determine the parameters affecting metabolic syndrome. In addition, a screening test for the parameters, supposed to affect MS, were performed.

Results

No statistically significant difference was found between mean ages of males and females ($p > 0.05$) the prevalence of MS was found to be significantly higher in females than in males ($p<0.05$). BMI, HDL and Cu levels were found to be significantly higher in women compared to men (for three of them $p< 0,001$). Zn level was found to be statistically higher in men than in women. ($p<0,001$). Other parameters were not found to be different between sexes.

Table1: Sex and age distribution of the cases

	n	%	Mean age
Male	90	22	41.5±13.33
Female	320	78	42.64±13.70
Overall	410	100	42±13.52

Table 2: MS positivity according to NCEP-ATP III criteria

	MS POSITIVITY
Male (n,%)	30, %33.3
Female (n,%)	147, %45.9

We determined cut-off values of hs-CRP, Cu and Zn to find values increasing the risk of MS. Cut-off value for Cu was determined as 16.5 ($p<0,001$), for Znas12.45 ($p>0.05$) and for hs-CRP as 2.335 ($p<0,001$). Then, hs-CRP, Cu and Zn were compared with each other in terms of predicting MS and MS parameters. After this

comparison, it was established that blood Copper level is similar to hs-CRP and predicted MS and MS parameters like hs-CRP does. But this prediction occurred different MS parameters at different sensitivities and specifies. We observed that there was a more significant correlation between TG level, blood pressure and Cu, compared to hs-CRP.

Table 3: Mean biochemical parameters and anthropometric measurements

	Male (n =90)	**Female** (n =320)	**P**
BMI (kg/m^2)	27.11±4.90	29.72±6.10	<0,001
Waist circumference (cm)	96.17±13.04	95.84±15.57	>0,05
Fasting blood glucose (mg/dL)	99.34±33.2	103.91±43.29	>0,05
Postprandial blood glucose (mg/dL)	123.84±57.85	131.98±72.44	>0,05
HDL-cholesterol (mg/dL)	45.93±11.4	54.16±13.05	<0,001
Trygliceride (mg/dL)	164.73±112.50	140.11±116.46	>0,05
Insulin (mU/ml)	9.26±6.43	9.53±8.42	>0,05
HOMA	2.32±1.88	2.39±2.20	>0,05
Systolic blood pressure (mmHg)	131.92±23.77	138.60±30.18	=0,053
Diastolic blood pressure (mmHg)	84.11±16.37	87.68±18.05	>0,05
hsCRP (mg/L)	2.75±2.22	2.93±2.32	>0,05
Cu mg/dL	14.68±2.81	17.30±3.48	<0,001
Zn mg/dL	13.31±2.76	12.52±2.20	<0,001

Discussion

MS is a chronic inflammatory event and CRP is the marker of inflammation. Thus, it has been accepted that hs-CRP is a good marker to predict MS and its parameters (1). But hs-CRP levels increase with acute inflammation and inflammation related chronic diseases (e.g. rheumatoid arthritis) and becomes hard to make an accurate prediction. It has been suggested that oxidative stress is related to MS and atherosclerosisand may also contribute to pathogenesis of insulin resistance (2). Cu and Zn are the components of SOD, which is an antioxidant enzyme. Thus, we think that Cu and Zn may be alternative markers to hs-CRP to predict MS, its parameters and atherosclerosis. In our study we detected that Cu levels in the patients, having MS and its components were significantly high but there were no significant changes in Zn levels. We found out a positive and statistically significant relationship between Cu and hs-CRP. We can also say that Cu predicts MS and it components and since it is not affected by the inflammatory process as much as CRP. In this term it can be accepted as a better marker for MS and atherosclerosis. MS is an inflammatory event in which free radicals increase. The increase in free radicals may cause the over use SOD enzyme and consequently changes in serum levels of Cu and Zn, which are among the components of this enzyme. Likewise, in our study, Cu levels in the patients with MS was found to be significantly high while there were no significant changes in Zn levels.

Fe and Cu participate in the fenton reaction in the tissue. The free electrons generated in the reaction increase cell membrane lipid peroxidation and cell damage. Thus, Fe and Cu participate in process of lipid peroxidation. High levels of Fe and Cu indicate increased lipid peroxidation and oxidative stress accordingly (9). Salonen et al. showed that lipid peroxidation in the patients with increased Cu level had a negative effect on blood vessel wall. All the studies suggested that these patients had four time higher risk of acute myocardial infarction than the normal population (10). Based upon these results, it may be stated that Cu predicts MS and MS parameters as well as hs-CRP does and that it is even a better predictor for MS and atherosclerosis since it is less influenced from inflammatory events than CRP. The mechanism of the significant positive relation between Cu, which is one of the cofactors of SOD, and MS and components of MS still remains to be completely known.

We think that the relation between copper, MS and atherosclerosis is an issue deserving investigation and further studies on this subject are required.

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Acknowledgement:
No funding received

Disclosure:
None declared

How to cite:

Yanardağ Açık D, Mescigil P.F, Sayiner Z.A. Do copper and zinc levels predict metabolic syndrome and metabolic syndrome's parameters as hs-CRP does? Gaziantep Med J 2015;21(3):196-199.