

The value of serum zinc, copper, ceruloplasmin levels in patients with gastrointestinal tract cancers

Gastrointestinal sistem kanserli hastalarda serum çinko, bakır ve seruloplazmin düzeylerinin önemi

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Background/aims: Gastrointestinal cancers are frequent diseases of particular importance for surgeons with regard to their management and follow-up. Neoplastic diseases activate antioxidant defense systems. As a result, concentrations of redoxal enzymes and their co-factor elements appear to change. The levels of zinc (Zn), copper (Cu) and ceruloplasmin have been found to be critical parameters. In addition, it seems to be important to consider the Cu/Zn ratio in such cases. In this study, changes in the levels of Cu, Zn and ceruloplasmin in patients with gastrointestinal system cancers was evaluated, and the proportion of Cu to Zn (Cu/Zn) is discussed. **Methods:** In this clinical trial, levels of Cu and Zn were defined with calorimetric methods and ceruloplasmin levels were measured with immunohistochemical methods in a control group of 20 healthy individuals and in 25 patients who underwent surgery for gastrointestinal system cancer. The blood samples were taken preoperatively in gastrointestinal system cancer patients. **Results:** This study has shown that while the decrease in Zn levels and the increase in ceruloplasmin levels in patients with gastrointestinal system cancers were found to be significant ($p < 0.001$, $p = 0.014$) when compared to the control group, the increase in the level of Cu was also found to be significant ($p = 0.019$). In the patient group, the correlations between serum Cu and serum ceruloplasmin proved to be significant ($r = 0.991$, $p < 0.001$). The Cu/Zn ratio, when compared with Zn, ceruloplasmin and Cu, showed significant results ($r = 0.562$, $r = 0.500$, $r = 0.506$, $p < 0.001$). **Conclusions:** This study shows that serum Cu, Zn and ceruloplasmin levels show changes in gastrointestinal system cancers, but further research is needed to demonstrate the importance and significance of these parameters and their relation with other contributing neoplastic factors.

Key words: Zinc, copper, ceruloplasmin, gastrointestinal system, cancers

INTRODUCTION

Essential elements copper (Cu) and zinc (Zn) have a role in many biochemical reactions as a micro-source (1). Zn stimulates gene transcriptions and cell multiplication. Increased Zn concentration levels might help multiplication of tumor cells (2).

Amaç: Gastrointestinal sistem kanserleri hem tedavi hem de takip açısından cerrahlar için önemli ve sık karşılaşılan bir hastalık grubudur. Neoplastik hastalıklar antioksidan defans mekanizmalarını aktive ederler, bunun sonucunda redoks enzimler ve kofaktör elementler değişikliğe uğrarlar. Serum bakır, çinko ve seruloplazmin düzeyleri bu hastalarda değerli parametreler olabilir. Çalışmamızda gastrointestinal sistem kanserli hastalarda serum bakır, çinko, seruloplazmin düzeyleri değerlendirilmiş ve Cu/Zn oranının önemi tartışılmıştır. **Yöntem:** Bu randomize klinik çalışmada serum Cu/Zn oranı kalorimetrik yöntemlerle, seruloplazmin düzeyleri ise immüno-kimyasal yöntemle değerlendirildi. Çalışma grubu 20 sağlıklı birey ve cerrahi planlanan 25 gastrointestinal sistem kanserli hastadan oluştu. Kan örnekleri preoperatif dönemde alındı. **Bulgular:** Çalışmamızda gastrointestinal sistem kanserli hastalarda kontrol grubuna göre serum Zn düzeylerinde azalma olurken, seruloplazmin düzeylerinde artış belirgin olarak görülmüştür. ($p < 0.01$, $p = 0.019$). İki grup karşılaştırıldığında serum bakır düzeylerindeki artışta, kanserli hasta grubunda istatistiksel olarak anlamlı idi ($p = 0.019$). Hastalıklı grupta; serum bakır ve seruloplazmin yükseklikleri belirgin olarak korelasyon gösterdi. ($r = 0.991$, $p < 0.001$). Hastalıklı grupta serum parametreleri Cu/Zn oranı ile karşılaştırıldığında daha anlamlı sonuçlar elde edildi. ($r = 0.562$, $r = 0.500$, $r = 0.506$, $p < 0.001$). **Sonuç:** Çalışmamızda, gastrointestinal kanserli hastalarda serum bakır, çinko ve seruloplazmin düzeylerinde değişikliklerin olduğu görülmüştür. Ancak bu parametrelerdeki değişikliklerin, diğer neoplastik faktörlerle ilişkilerini gösterebilmek için daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Bakır, çinko, seruloplazmin, gastrointestinal sistem, kanser

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Manuscript received: 20.01.2004 **Accepted:** 15.03.2005

rum concentration levels are found to be increased in leukemia (5), lymphomas, sarcomas, bronchiogenic carcinomas, melanomas and gynecological cancers (6, 7), ceruloplasmin levels are found to be increased in breast, cervix and endometrium cancers and oral leukoplakia (7, 8). Ceruloplasmin is a copper-carrying glucoprotein. It uses ferric oxidase activity to prevent the occurrence of toxic Fe products. In addition, it controls membrane lipid oxidation (9). As an acute phase reactant, ceruloplasmin was found to be increased in gastrointestinal (GIS) cancers (10, 11). In fact, it is claimed to be a prognostic and diagnostic factor in various malignancies (12). In contrast, Zn is found to be decreased in GIS, breast and other similar cancers (1, 4, 13). In this study, serum Zn, Cu and ceruloplasmin levels were measured in patients operated for GIS cancer. The relations between each factor were studied to determine the importance of these parameters in malignant illnesses.

MATERIALS AND METHODS

This study was performed in the Clinical Biochemistry and General Surgery Departments of SSK Izmir Teaching Hospital. The study group (Group 1) consisted of 25 (17 males, 8 females; median age 57 years, range 25-75) GIS cancer patients who were followed in the General Surgery Department. The healthy control group (Group 2) consisted of 20 people (11 males, 9 females, median age 53 years, range 25-64). In Group 2, the subjects had no clinical or biochemical complaints or abnormalities. The serum Zn, Cu and ceruloplasmin levels were tested preoperatively and compared with a healthy population. These blood samples were centrifuged, put into tubes with pure gel, and kept at -70°C. Patients using oral contraceptives, those with diarrhea, active hemorrhagic attacks and diabetes mellitus were excluded from this study. Serum ceruloplasmin was assessed using the immunohistochemical rate nephelometer technique on the Beckman 360 array protein system (Beckman Instruments Inc, Brea, CA, USA). For standardization purposes, all the calibrators, controls and tampons were obtained from the same company. Serum Cu and Zn levels were assessed by calorimetry using a protein aggregation technique on Böhlinger-Manheim 4010 photometer with a Randox kit. Statistical evaluation was carried out using SPSS 10.0 statistical program. Groups were compared with Mann-Whitney U test. The relationship between correlations was measured using Spearman's rank coefficient of correlation (CC).

RESULTS

The type of GIS tumors were as follows: 3 gastric cancer (T3N1Mo), 2 pancreas cancer (T4N2M1) and 20 colon cancers (10 with Duke's B2, 10 with Duke's C). All patients were operated electively without any obstruction or complication. The demographics of the control and study groups were not statistically different. In the study group, cancer cachexia was present in five patients who had advanced pancreas and gastric cancer and these patients all died at a mean of 11 months after operation. Even though there was a minimal increase in serum Cu levels in Group 2, it was also statistically significant compared with Group 1 (Table 1,

Table 1. Serum copper levels (µg/dl)

	N	Mean±SD	Median (Min-Max)
Group 1 (GIS Cancer)	25	170±23,31	164,3 (133,2-214,6)
Group 2 (Control)	20	153,57±15,92	164,3 (127-185)
P=0,019			

p=0.019). In Group 1, levels of serum ceruloplasmin were found to be significantly increased (Table 2, p=0.014) and levels of serum Zn were found to be significantly decreased (Table 3, p<0.001). In addition, the correlation between serum ceruloplasmin and serum Cu was found to be signifi-

Table 2. Serum ceruloplasmin levels (µg/dl)

	N	Mean±SD	Median (Min-Max)
Group 1 (GIS Cancer)	25	46,62±12,35	45,2 (29,69)
Group 2 (Control)	20	37,42±8,25	35,7 (25,5-53)
P=0,014			

cant (r=0.991, p<0.001) (Figure 1). There was also a significant difference between the Cu/Zn ratio in Groups 1 and 2 (Table 4, p<0.001). However, in Group 1, the relation between the Cu/Zn ratio and Zn, Cu, and ceruloplasmin was found to be significant (r=0.562, r=0.500, r=0.506, p<0.001, respectively) (Figure 2).

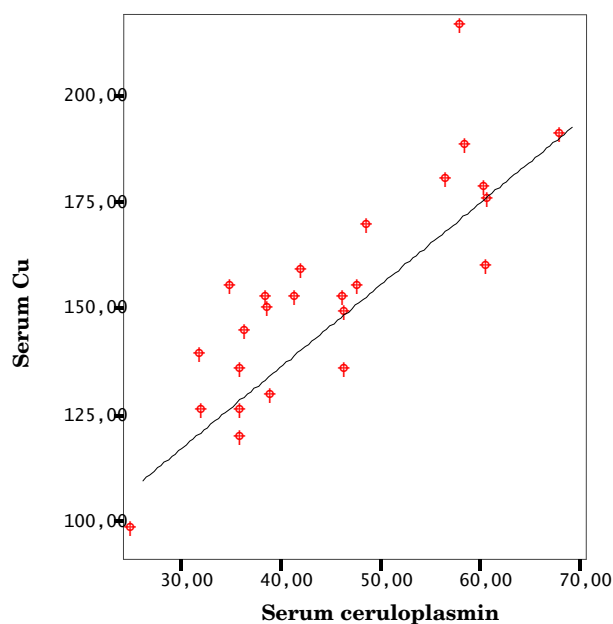
Table 3. Serum zinc levels (µg/dl)

	N	Mean±SD	Median (Min-Max)
Group 1 (GIS Cancer)	25	129,30±13,39	128,8 (102,2-154,8)
Group 2 (Control)	20	154,11±18,98	153,6 (123-187,4)
P=0,001			

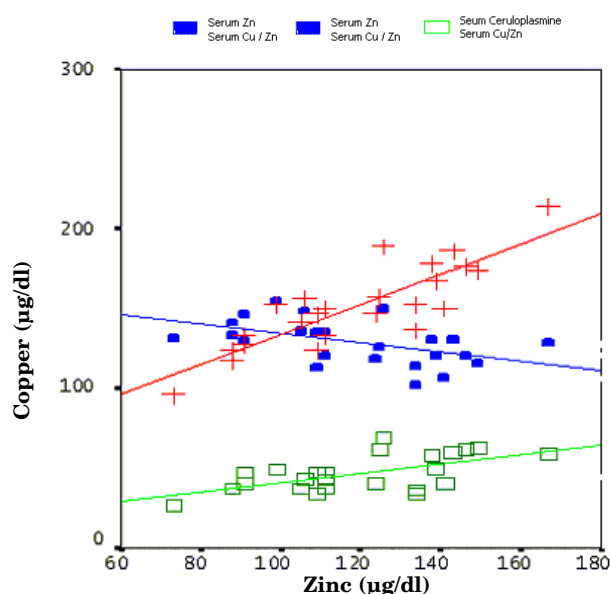
Table 4. Cu/Zn ratio

	N	Mean \pm SD	Median (Min-Max)
Group 1 (GIS Cancer)	25	1,31 \pm 0,06	1,28 (1,22-1,43)
Group 2 (Control)	20	0,99 \pm 0,03	0,99 (0,94-1,05)

P=0,001



r = 0.823, p < 0.001

Figure 1. Correlation between serum copper and ceruloplasmin

r = -0.558, r = 0.799, r = 0.533 (p < 0.001)

Figure 2. Relation between the Cu/Zn ratio and Zn, Cu and ceruloplasmin

DISCUSSION

Ceruloplasmin is an enzyme which has a role as an oxidant or antioxidant depending on the existence of Fe ions and similar material levels in the micro base. It also stops lipid peroxidation by direct oxidation of cations. As a result, membrane lipid oxidation is controlled (9, 14). Recently, the antioxidant defense system that affects the occurrence and advancement of neoplastic illnesses has been under research. This defense system consists of co-factors which are element enzymes and low-weighted molecular compounds (1). Ceruloplasmin makes up 95% of the total Cu contained in these isotopic elements. Cu makes up the main compound of the metalloproteins responsible for oxidation-reduction reactions (9, 14). Zn is essential for the development of, for example, nucleic acid and protein synthesis (15). In addition, Zn ensures the stability of the fullness of the 'd' orbital, and this makes oxidation-reduction impossible in any environment containing Zn (9).

The high levels of serum ceruloplasmin with GIS cancer have been reflected in recent studies (2, 10, 11, 14). Ceruloplasmin has been found in some studies to be a diagnostic factor (8, 10). In our study, the value of serum ceruloplasmin with GIS cancer patients was found above the level of the control group, but below the predicted levels. As a result, it was decided to form a reference group. Although some publications defend the possibility that ceruloplasmin may increase due to the fact that it is an acute phase protein, there is no definite conclusion on this subject. Some studies support the possibility of an increase of oxidative stress reduction in the nature of the cancer related to a ceruloplasmin prognosis (8).

It has been postulated that CA 15-3 and ceruloplasmin levels were positively correlated in the follow-up of patients with breast cancer (16). Other results also showed that the three different molecules were all able to induce angiogenesis provided they were bound to Cu. Fragments of the ceruloplasmin molecule also induced angiogenesis but only when Cu was bound to the peptides. The data are interpreted to indicate that Cu ions are involved in the sequence of events leading to angiogenesis and that the carrier molecules may be of quite a different nature (12, 17).

The serum Cu levels were found to be higher in cancer patients than in the control group (p = 0.019). However, the decrease in Zn levels was fo-

und to be significant ($p < 0.001$). In some publications, an increase in serum Cu and a decrease in Zn in breast cancers and gynecological cancers were decided to be prognostic and diagnostic factors (6, 17-19). These factors have not been extensively studied in GIS cancers (1, 11). While the decrease in Zn levels in diseases with benign characteristics appears to be less than in normal cancer cases (1), with malignancy, Zn levels drop more (8). In our research, the decrease in Zn levels seems to correlate with the strength of the cancer in the patient group. In addition, the decrease in Zn levels alone as a prognostic index of cancer is still under discussion in the literature (13, 20). In our study, the levels of Zn, Cu and ceruloplasmin were compared with the Cu/Zn ratio. A significant correlation in the patient group ($r = -0.562$, $r = 0.500$, $r = 0.506$, $p < 0.001$) was found. As a result, instead of analyzing the effects of Cu, Zn and ceruloplasmin individually, it was found to be important to evaluate them in relation to the Cu/Zn ratio in the

monitoring of the trace elements in cancer patients. We also found that the Cu/Zn ratio in cancer patients was higher than in the control group ($p < 0.001$). There is other literature available to support our findings (7). It was found that there was no correlation between the ultrafiltrated Cu and serum total Cu levels and serum ceruloplasmin levels. In the literature referring to rectal cancers, some authors have found similar results for Cu but not for Zn (1, 9). The proportion of these elements varies between different cancer types. There is also a variety even within GIS cancers. This points to the fact that there must be other contributing factors in neoplastic diseases. It is therefore necessary to carry out further research into these factors.

In conclusion, serum Cu, Zn and ceruloplasmin levels show changes in GIS cancers, but further research is needed to show the importance and significance of these parameters and their relation with other contributing neoplastic factors.

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