

# The Relationship Between Serum Zinc Levels and Tumor Markers in Hemodialysis Patients

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## ABSTRACT

The incidence of neoplasia is increased in end-stage renal disease (ESRD) patients. Zinc (Zn) deficiency is associated with neoplasia and also commonly seen in ESRD patients. However, the data regarding the relationship between Zn levels and tumor markers is scant in this population. We aimed to investigate the relationship between Zn levels and tumor markers in hemodialysis patients. Twenty-six hemodialysis patients (11 male, 15 female, mean age 41.6±14.3 years) and 11 healthy subjects (6 male and 5 female, mean age 38.7±7.2 years) were included. Serum Alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), CA 19-9, CA 15-5, CA 125, beta subunit of human chorionic gonadotrophin (B-HCG) and beta-2 microglobulin (B2M) and Zn levels were measured. Data were analysed by Student's t test. Serum Zinc levels were significantly lower in ESRD patients (group 1) compared to healthy subjects (group 2) ( $p<0.0001$ , for all). Serum CEA and B2M levels were also significantly higher in group 1 patients compared to group 2 subjects ( $p<0.005$ ,  $p<0.0001$ , respectively). Serum Ca15-3 and CA-125 levels were found to be significantly lower in group 1 patients compared to group 2 subjects ( $p<0.005$ ,  $p<0.001$ , respectively). There were no statistically significant difference in terms of serum CA 19-9, B-HCG and AFP between group 1 and group 2 patients. In group 1 patients, there was a negative correlation between serum Zn levels and AFP, while a positive correlation was observed between serum Zn levels and CA15-3. The measurement of AFP may be beneficial in HD patients. Further studies are needed.

**Key words:** Hemodialysis, zinc, tumor markers

## Hemodiyaliz hastalarında Serum Çinko Seviyeleri ile Tümör Belirteçleri

### ÖZET

Son dönem böbrek yetersizliği (SDBY) bulunan hastalarda neoplazi insidansı artmıştır. Çinko (Zn) eksikliği neoplazi gelişimi ile ilişkilidir ve bu durum SDBY hastalarında sıklıkla görülmektedir. Bununla birlikte bu popülasyonda serum Zn düzeyleri ile tumor belirteçleri arasındaki ilişki bilinmemektedir. Çalışmamızda hemodiyaliz hastalarında serum Zn düzeyleri ile tümör belirteçleri arasındaki ilişkiyi araştırmayı hedefledik. Çalışmaya 26 hemodiyaliz hastası (11 erkek, 15 kadın, yaş ortalaması 41.6±14.3 yıl) ve 11 sağlıklı birey (6 erkek, 5 kadın, yaş ortalaması 38.7±7.2) dahil edildi. Serum alfa fetoprotein (AFP), karsinoembriyonik antijen (CEA), CA 19-9, CA 15-5, CA 125, beta HCG, beta-2 mikroglobulin (B2M) ve Zn değerleri ölçüldü. Veriler Student t test ile analiz edildi. Serum Zn düzeyleri SDBY hastalarında (grup 1) sağlıklı bireylere (grup 2) oranla anlamlı olarak düşük saptandı ( $p<0.0001$ ). Serum CEA ve B2M düzeyleri grup 1 hastalarda anlamlı olarak yüksekti (sırasıyla,  $p<0.005$  ve  $p<0.0001$ ). Serum Ca15-3 and CA-125 düzeyleri ise grup 1 hastalarda anlamlı olarak düşük saptandı (sırasıyla,  $p<0.005$  ve  $p<0.001$ ). Her iki grup arasında serum CA 19-9, B-HCG ve AFP açısından anlamlı fark yoktu. Grup 1 hastalarda serum Zn seviyesi ile AFP arasında pozitif korelasyon ve CA 15-3 arasında negatif korelasyon vardı. Hemodiyaliz hastalarında AFP ölçümü faydalı olabilir. Bu konuyla ilgili detaylı çalışmalara ihtiyaç vardır.

**Anahtar kelimeler:** Hemodiyaliz, çinko, tümör belirteçleri

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## INTRODUCTION

Zinc (Zn) deficiency is a leading cause of diseases in developing countries (1). Hemodialysis (HD) patients are at risk for both deficiency and accumulation of trace elements including zinc (Zn), depending on dietary intake, removal by dialysis, the composition of the source water used for hemodialysis and residual kidney function (2-3). Zinc deficiency is associated with delayed wound healing (4), and immune deficiency characterized by impaired cell proliferation, abnormal T-cell function, defective phagocytosis, and abnormal cytokine expression (5-6), all of which might contribute to the excess risk of infection observed in hemodialysis patients (7-9).

The incidence of neoplasia is increased in patients with end-stage renal disease (ESRD) receiving HD (10). Tumor markers are useful to exclude active malignant diseases in the candidates for transplantation and ESRD patients receiving HD (11). Zn deficiency is also commonly seen in end-stage renal disease patients (12). Serum Zn levels were found to be associated with some malignancies including head, neck and esophagus cancer (13-14). Hence, we aimed to investigate the relationship among serum Zn levels and tumor markers including, alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), CA 19-9, CA 15-5, CA 125, beta subunit of human chorionic gonadotrophin ( $\beta$ -HCG) and beta-2 microglobulin ( $\beta$ 2M) in hemodialysis patients.

## MATERIALS AND METHODS

Twenty-six hemodialysis patients (Group 1) and 11 healthy subjects (Group 2) were included in this cross-sectional study. Among the 26 patients in Group 1, 11 were male and 15 were female with the mean age of  $41.6 \pm 14.3$  (21-67 years). The patients had been on hemodialysis for  $66.3 \pm 8.1$  months. None of the patients

and healthy subjects had clinical evidence of malignancy. Among the 11 healthy subjects in group 2, 6 of them were male and 5 of them were female with the mean age of  $38.7 \pm 7.2$  (26-45 years).

HD patients were receiving thrice-weekly dialysis for a 4-h period with a standard bicarbonate-containing dialysate bath using a biocompatible HD membrane (Polysulfone, FX-80 series, Fresenius, Germany). Dialysate flow rates were 500 ml/min and blood-flow rates were 250-300 ml/min. Venous blood samples for biochemical analyses were drawn after an overnight fast between 8:00 pm and 8:00 am at a single midweek dialysis sessions. In all of the cases, serum Zn levels and the following tumor markers measured; AFP, CEA, CA 19-9, CA 15-5, CA 125,  $\beta$ -HCG and  $\beta$ 2M. Serum Zn levels were measured by atomic absorption spectrophotometry. Tumor markers were measured in the serum by solid-phase, two site chemiluminescent enzyme immunometric assay.

The study protocol was approved by the Medical Ethics Committee of Istanbul University (Istanbul School of Medicine, Istanbul, Turkey). Written informed consent was obtained from all subjects included in the study.

### Statistical Analysis

Data were entered into an electronic based SPSS statistical program. The results were analyzed by means of Students' t test and correlation analysis. Data are expressed as mean  $\pm$  SD. The significance was set at  $p < 0.05$ .

## RESULTS

Serum zinc and tumor marker levels of ESRD patients and healthy subjects were shown in table 1. Serum Zinc levels were significantly lower in ESRD patients (group

**Table 1.** Serum zinc, and tumor marker levels of ESRD patients and healthy subjects

Parameters	Group 1(n:26)	Group 2(n:11)	p values
Zinc ( $\mu$ g/dL)	107.13 $\pm$ 21.58	206.91 $\pm$ 25.38	<0.0001
AFP(IU/mL)	0.67 $\pm$ 0.29	0.81 $\pm$ 0.27	>0.05
CEA(ng/mL)	4.45 $\pm$ 3.87	0.86 $\pm$ 0.70	<0.005
CA 19-9 (U/mL)	26.13 $\pm$ 36.46	10.01 $\pm$ 8.00	>0.05
CA 15-3 (U/mL)	21.0 $\pm$ 14.17	44.17 $\pm$ 19.58	<0.005
CA 125 (U/mL)	5.07 $\pm$ 2.93	9.01 $\pm$ 6.01	<0.01
$\beta$ -HCG (mIU/mL)	6.15 $\pm$ 7.13	4.26 $\pm$ 2.03	>0.05
$\beta$ 2M (ng/mL)	32445 $\pm$ 13585	1667 $\pm$ 421	<0.0001

**Table 2.** The correlations between serum Zn levels and associated parameters in group 1 patients

Parameters	r value	p value
AFP	-0.62	<0.05
CEA	-0.24	>0.05
CA 19-9	-0.25	>0.05
CA 15-3	0.67	<0.05
CA 125	-0.09	>0.05
B-HCG	-0.32	>0.05
B2M	0.27	>0.05

1) compared to healthy subjects (group 2) ( $p < 0.0001$ , for all). Serum CEA and B2M levels were also significantly higher in group 1 patients compared to group 2 subjects ( $p < 0.005$ ,  $p < 0.0001$ , respectively). Serum Ca15-3 and CA-125 levels were found to be significantly lower in group 1 patients compared to group 2 subjects ( $p < 0.005$ ,  $p < 0.001$ , respectively). There were no statistically significant difference in terms of serum CA 19-9, B-HCG and AFP between group 1 and group 2 patients.

In group 1 patients, there was a negative correlation between serum Zn levels and AFP, while a positive correlation was observed between serum Zn levels and CA15-3.

In group 2 patients, there were no correlation between serum Zn levels and tumor markers.

## DISCUSSION

There is a high incidence of neoplasia in renal transplant recipients and in CKD patients (15-16). Tumor markers are useful in the detection of various neoplasias but their sensitivity and specificity is controversial in this population (11, 17). Since the metabolism and clearance of these substances may be affected in renal failure, their serum levels may be found to be elevated in

**Table 3.** The correlations between serum Zn levels and associated parameters in group 2 patients

Parameters	r value	p value
AFP	-0.13	>0.05
CEA	-0.06	>0.05
CA 19-9	-0.03	>0.05
CA 15-3	0.029	>0.05
CA 125	0.022	>0.05
B-hCG	0.32	>0.05
B2M	0.07	>0.05

uremic patients without underlying malignancy.

In our study, serum levels of CEA and B2M were significantly elevated in hemodialysis patients compared to healthy subjects. In the literature, there are conflicting results regarding serum CEA levels after HD treatment. Polenakovic et al. (18) showed that the mean values of CEA did not exceed the upper limit of normal values in chronic HD patients. Menzin et al. (19) also demonstrated that there were no difference in terms of serum CEA levels between pre and post hemodialysis periods. However, according to various study results, serum CEA levels strongly tend to duplicate after HD treatment (15, 20-21). Eskiocak et al. (22) demonstrated that serum CEA levels were significantly higher in HD patients compared to healthy subjects and CKD patients. The results of these studies were in accordance with the present study.

Tzitzikos et al. (15) have shown that serum CA 19-9 levels were increased after HD, however there was no difference in the serum levels of CA 19-9 in our study. In our study, serum levels of CA 15-3 and CA 125 were found to be higher in control subjects compared to HD patients, however, these results in both groups were within the normal limits. There are several malign and benign conditions that serum CA 15-3 levels were increased. Tzitzikos et al. (15) found 13% of their HD patients had higher CA 15-3 levels than other. They concluded that the increased serum levels of CA 15-3 were probably due to the concomitant hepatitis C infection. Although, Camci et al. (23) demonstrated that HD patients had significantly elevated levels of serum CA 125 levels, there were also studies showed that these increased levels were attributed to gender.

Tzitzikos et al. (15) recently showed that serum AFP levels remained unaltered after the HD session, a finding which was also in accordance with our results and other studies. Eskiocak et al. (22) demonstrated that serum B-HCG levels were significantly higher in HD patients compared to healthy subjects and CKD patients. According to our study results, the serum B-HCG levels were found to be higher in HD patients when compared to healthy subjects. However, the values were not found to be statistically significant between 2 groups. Zinc deficiency is prevalent world wide especially in developing countries and may affect nearly 2 billion subjects (24). The major manifestations of include growth retardation, hypogonadism, cell-mediated immune dysfunctions,

and cognitive impairment (25). Zinc also functions as an antioxidant and anti-inflammatory agent (26). Oxidative stress and chronic inflammation have been implicated in development of many cancers including head, neck and esophagus cancer (13-14). Ananda et al. (24) showed that nearly 65% of these patients were zinc deficient based on their cellular zinc concentrations.

In a metaanalysis, Tonelli et al. (12) found that hemodialysis patients appear to have lower levels of zinc and selenium than people in the general population. In group 1 patients, serum Zn levels were markedly decreased compared to group 2 patients. In the present study, the correlation analysis showed a positive correlation between serum Zn levels and CA15-3 and a negative correlation between serum Zn levels and AFP in hemodialysis patients. On the other hand, no correlation was observed between serum Zn levels and tumor markers in healthy subjects.

Our study has some limitations; first, this is a cross sectional analysis of ESRD patients regarding the relationship between serum zinc levels and tumor markers. Second, the sample size was relatively small. In conclusion, the measurement of some of the tumor markers including alfa-feto protein and B-HCG may be beneficial in HD patients. Repletion of the zinc may be beneficial to prevent various cancers in this population. Concerning the controversial results reported in the literature, further detailed investigations about this subject are needed.

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