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Serum Copper and Zinc Levels in Patients with Endometrial Cancer

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Abstract

The aim of the present study was to evaluate serum concentrations of copper (Cu) and zinc (Zn), in relation with metabolic profile and clinicopathologic features of patients with endometrial cancer. A total of 47 women with endometrial cancer and 45 controls were eligible for the study. Clinicopathologic features and metabolic profile as well as serum copper and zinc levels were evaluated in each subject. Patients with endometrial cancer (Cu mean 3.72 ± 2.15 mg/L, median 3.54 [0.41–9.16] mg/L and Zn mean 1.83 ± 0.71 mg/L, median 1.77 [0.71–4.02] mg/L) exhibited lower Cu and Zn levels than those of controls (Cu mean 6.06 ± 1.79 mg/L, median 6.32 [2.95–9.05] mg/L and Zn mean 2.48 ± 0.89 mg/L, median 2.23 [1.23–4.54] mg/L) ($p < 0.001$). Cu/Zn ratio was also higher (0.85 ± 1.96 vs. 2.57 ± 0.73) in controls as compared with patients with endometrial cancer. While Cu levels showed no significant correlation with age, body mass index, gravidity, and parity, a positive correlation was found between Zn levels and parity. When cancer patients were evaluated on their own, both Cu and Zn levels showed positive correlation with age. Additionally, the cancer patients with myometrial invasion > 1/2 exhibited lower Cu levels compared with the cancer patients with myometrial invasion < 1/2. The data of the present study suggested that women with endometrial cancer are characterized by altered serum Cu and Zn levels as compared with controls. Imbalance of these trace element levels might be associated with endometrial cancer among Turkish patients.

Keywords Endometrium · Cancer · Copper · Zinc

Introduction

Endometrial cancer is the most common gynecologic malignancy and the forth most common cancer among women [1]. Comprehensive understanding of epidemiology, pathophysiology, and diagnostic and management strategies for endometrial cancer allows the clinician to identify women with high risk of cancer development, contribute to risk reduction, and facilitate early diagnosis [2]. Endometrial cancer is classified into two types that differ in epidemiology, genetics, prognosis, and treatment: (1) type 1, or endometrioid adenocarcinoma, is the most common histologic type of endometrial cancer and accounts for more than three-fourths of all cases, and (2) type 2 is characterized by clear cell and papillary serous tumor histologies. Most cases of type 1 cancer are low grade and confined to the uterus at diagnosis [2].

From biomedical perspective, trace elements are fundamental micronutrients which take part in several important biological mechanisms such as functioning as cofactors of antioxidant enzymes, cell proliferation, and differentiation. Imbalances in levels of trace elements may affect human health in a disadvantageous manner. There is a subtle balance between free radical generation and the antioxidant defense in healthy conditions. Oxidative stress may occur in the event of alteration in optimal levels of trace elements causing metabolic disturbances and changes in the cellular structure [3]. Exposure to reactive oxygen radicals can cause DNA damage, mutation, and carcinogenesis on the basis of altered trace element levels [3, 4].

Copper (Cu) and zinc (Zn) are two minor biological elements that have critical roles as cofactors for various enzymatic reactions for antioxidant defense, DNA repair and integrity, cell division, as well as protein synthesis [3]. They are the

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components of Cu/Zn superoxide dismutase, an important antioxidant enzyme for cellular protection from reactive oxygen species.

Although Zn and Cu concentrations in serum and tissue samples of patients with and without various cancers such as colon [3], bladder [4], thyroid [5], breast [6], gynecologic [7], and oral [8] cancers are evaluated in the scientific literature, there are very few data regarding the effect of Cu and Zn on endometrial cancers. Cu/Zn ratio and systemic oxidant load have clinical importance for aging-related degenerative diseases, nutritional status, oxidative stress, inflammation, and immune abnormalities [9–11] which may affect carcinogenesis. Ever use of intrauterine devices (IUD) containing Cu was found to be inversely associated with endometrial cancer risk, independent of known risk factors in a recent paper [12]. There is also no previous study evaluating the serum trace element levels in endometrial cancer in the literature. Therefore, the present study aimed to investigate serum Cu and Zn levels in patients with and without endometrial cancer. This study is also set out to correlate serum trace element levels in relation with metabolic and cardiovascular profile and clinicopathologic features of patients with endometrial cancer.

Materials and Methods

The design of the present study was approved by the Ethical Committee and Institutional Review Board of Adnan Menderes University Faculty of Medicine, where the study was conducted. Written informed consents were obtained from all participants.

Patients

Forty-seven women with a histological confirmed diagnosis of endometrial cancer after uterine curettage and surgery were eligible for the study group. Forty-five women, who underwent endometrial curettage because of abnormal uterine bleeding, were diagnosed dysfunctional uterine bleeding without any organic gynecologic pathology and history of any kind of cancer constituted the controls. None of the patients in the study group had undergone radiotherapy or chemotherapy prior to surgery. Detailed clinical history examining diabetes mellitus (DM), hypertension, and smoking was taken for all participants. Body mass index (BMI) was also calculated. All of the patients with endometrial cancer diagnosis underwent surgery including peritoneal washing, total abdominal hysterectomy, bilateral salpingo-oophorectomy. The general attitude of the study center towards endometrial cancer detected by endometrial curettage is to perform frozen investigation in order to evaluate myometrial invasion degree, so that intraoperative frozen investigation was performed to all patients. The patients with ≥ 1/2 myometrial invasion and/or grade 3 histologic degrees underwent staging surgery involving omentectomy, and pelvic, para-aortic lymphadenectomy. Staging assignment was made according to the International Federation of Gynecology and Obstetrics (FIGO) for endometrial cancer [13]. Architectural grading was based on the degree of glandular differentiation in accordance with the FIGO guidelines.

Instrumentation

A 5-mL sample of venous blood was collected in a metal free sterile tube from all participants. After centrifugation at 3000 rpm for 10 min to extract serum, the serum samples without sign of hemolysis were taken into Eppendorf tubes and stored at − 80 °C until assayed. Levels of Cu and Zn in the serum were determined using a flame atomic absorption spectrometer (the Varian SpectrAA 220 FS [Fast Sequential], Australia). The material was not digested. It was diluted with distilled water tenfold before the analysis. Reference material for Cu and Zn standard was obtained from Merck for AAS and dissolved in distilled water. Standard concentrations for Cu were 0.75, 1.5, 3, 4.5, and 6 ppm (mg/L). Standard concentrations for Zn were 0.3, 0.6, 0.9, 1.2, and 1.5 ppm (mg/L). Calibration was performed according to these standard solutions. Sample concentrations were calculated by standard curve equation. The wavelength for Cu was 324.8 nm, and the wavelength for Zn was 213.9 nm. Limit of detection for Cu 1.5 mg/L gives about 0.2 Abs at 324.8 nm, A/A burner. Limit of detection for Zn 0.3 mg/L gives about 0.2 Abs at 213.9 nm, A/A burner.

Statistical Analysis

Data analysis was performed by using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA). Whether the distributions of continuous and discrete variables were normal or not was determined by Kolmogorov–Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Continuous and discrete variables were shown as mean ± SD or median (min–max), where applicable. A number of cases and percentages were used for categorical data. While the mean differences between groups were compared by Student's t test, otherwise, Mann–Whitney U test was applied for comparisons of not normally distributed variables. When the number of independent groups was more than two, data analyses were performed by using one-way ANOVA or Kruskal–Wallis test, where appropriate. Categorical data were analyzed by continuity corrected chi-square test. Degrees of association between continuous variables were evaluated by Spearman's rank correlation analyses. Determining the best predictor(s) which affect on Cu and Zn measurements was evaluated by multiple linear regression analyses. Any variable whose univariable test had a p value < 0.10 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Coefficient of regression, 95% confidence intervals, and t-statistic for each independent variable were also calculated. Because of not normally distributed, logarithmic transformation was used for Zn measurements in regression analyses. A p value less than 0.05 was considered statistically significant.

Results

A total of 47 women with endometrial cancer and 45 controls participated in this study. All of the endometrial cancer cases were endometrioid type. Age and BMI were found to be higher in patients with endometrial cancer compared with controls ($p < 0.001$ and $p = 0.019$, respectively). Gravidity, parity, DM, hypertension, menopausal status, and smoking habits were comparable between groups ($p > 0.05$). Patients with endometrial cancer (Cu mean 3.72 ± 2.15 mg/L, median 3.54 [0.41–9.16] mg/L and Zn mean 1.83 ± 0.71 mg/L, median 1.77 [0.71–4.02] mg/L) exhibited lower Cu and Zn levels than those of controls (Cu mean 6.06 ± 1.79 mg/L, median 6.32 [2.95–9.05] mg/L and Zn mean 2.48 ± 0.89 mg/L, median 2.23 [1.23–4.54] mg/L) ($p < 0.001$). Cu/Zn ratio was also higher (0.85 ± 1.96 vs. 2.57 ± 0.73) in controls as compared with patients with endometrial cancer (Table 1; Figs. 1 and 2). Demographic, clinical, and biochemical characteristics of women with endometrial cancer and controls are summarized in Table 1.

The basic characteristics of the subjects with endometrial cancer are displayed in Table 2. All cases of endometrial cancers were endometrioid type. A total of 36.2% had grade 1 tumors, 57.4% had grade 2 tumors, and 6.4% had grade 3 tumors. Thirty-eight patients were classified as having stage 1 disease, whereas two patients stage 2, six patients stage 3, and only one patient as having stage 4 disease, according to the FIGO staging system (9).

When all subjects were evaluated, no significant correlation was found between Cu levels with age, BMI, gravidity, and parity ($p > 0.05$); however, Zn levels showed a positive correlation with only parity ($p = 0.039$, $r = 0.216$), but not with the other parameters ($p > 0.05$). When patients with endometrial cancer were evaluated on their own, both Cu and Zn levels exhibited positive correlation with only age ($p = 0.009$, $r = 0.378$ and $p = 0.011$, $r = 0.366$, respectively) while no correlation was found between trace element levels and BMI, gravidity, parity tumor size, tumor grade, and disease stage ($p > 0.05$). DM, HT, tumor grade, lymphovascular space involvement, menopausal status, and smoking habit were not effective on both Cu and Zn levels ($p > 0.05$). In controls, only BMI was positively correlated with Zn levels ($p = 0.009$). However, in patients with myometrial invasion ≥ 1/2, Cu levels were higher than those with myometrial invasion < 1/2 ($p = 0.039$). Zn levels were not affected by myometrial invasion status ($p > 0.05$) (Tables 3 and 4; Fig. 3).

While the age of the control and the case groups were different, it was investigated by multivariate linear regression analysis, if the modifying effect of the disease on Cu measurements persisted when adjusted for age. After adjustment for all confounding factors, it was observed that there was a decreasing effect of the disease on Cu levels, as the Cu levels continued to decrease in the study group independent of age ($B = -2.818$, 95% CI -3.658 to -1.978 and $p < 0.001$). Furthermore, univariate analysis showed that there was no significant modifying effect of age on Cu, but the Cu level increased as age progressed in view of whether the person was cancerous or not ($B = 0.072$, 95% CI 0.027–0.117 and $p = 0.002$) (Table 5). We also investigated if the modifying effect of the disease on Zn measurements persisted when adjusted for possible confounding factors. After adjustment for all confounding factors, it was observed that there was a decreasing effect of the disease on Zn levels as the Zn levels continued to decrease in the study group independent of age, BMI, and parity. Additionally, univariate analysis did not show a significant modifying effect between Zn levels and age, but as age progressed in view of whether the person was cancerous or not, it appears that Zn levels increase with age (Table 6).

Determining the best predictor(s) which affect on Cu measurements in cancer patients was also evaluated by multivariate linear regression analyses. Any variable whose univariable test had a p value < 0.10 was accepted as a candidate for the multivariable model along with all variables of known clinical importance (age, myometrial invasion, stage). Age is found to be a significant increasing factor on Cu levels independent of myometrial invasion and stage ($B = 0.107$, 95% CI 0.038–0.175 and $p = 0.003$). Table 7 shows that all possible factors may affect Cu levels in women with endometrial cancer with multiple linear regression model.

Discussion

The data of the present study revealed that Cu and Zn levels were lower in women with endometrial cancer compared with controls. Our results suggest that women with endometrial cancer are characterized by altered serum Cu and Zn levels as compared with controls. Imbalance of these trace element levels might be associated with endometrial cancer among Turkish patients.

Trace elements are essential micronutrients which are involved in several biological mechanisms taking functions as cofactors for the activity of antioxidant enzymes, cell division, and differentiation [3]. Cu, one of the trace elements, functions in red blood cell formation and takes several roles in activation of more than 30 enzymes including cytochrome and lysine

Table 1 Demographic, clinical, and biochemical characteristics of women with endometrial cancer and controls

	Endometrial cancer ($n = 47$)	Controls ($n = 45$)	p
Age (years)	57.8 ± 8.4	51.1 ± 9.1	*< 0.001*†
BMI (kg/m^2)	32.7 ± 6.7	29.8 ± 5.0	*0.019*†
Gravidity	3 (0–13)	4 (0–9)	0.458‡
Parity	2 (0–11)	2 (0–7)	0.699‡
Smoking (*n*)	4 (8.5%)	7 (15.6%)	0.472¶
DM (*n*)	10 (%21.3)	9 (20.0%)	> 0.999¶
Hypertension (*n*)	18 (38.3%)	15 (%33.3)	0.780¶
Menopausal status (*n*)			*< 0.001*¶
Premenopausal	11 (23.4%)	27 (60%)	
Postmenopausal	36 (76.6%)	18 (40%)	
Cu (mg/L)	3.72 ± 2.15	6.06 ± 1.79	*< 0.001*†
Zn (mg/L)	1.77 (0.71–4.02)	2.23 (1.23–4.54)	*< 0.001*‡
Cu/Zn ratio	0.85 ± 1.96	2.57 ± 0.73	*< 0.001*†

The p values indicating statistically significant values were written in italics

BMI body mass index, *DM* diabetes mellitus, *Cu* copper, *Zn* zinc

† Student's *t* test

‡ Mann–Whitney *U* test

¶ Continuity corrected chi-square test

oxidases, dopamine hydroxylase, and tyrosinase and is necessary for healthy connective tissue development. Deficiency of Cu may result in anemia, skeletal defects, nervous system degeneration, and reproductive failure [7]. Another trace element Zn is also necessary for DNA synthesis and cell proliferation; is an essential part of transcription factors, enzymes functioning in digestion, metabolism, reproduction, and wound healing; and is an antioxidant [7]. The body has a well-developed antioxidant system to neutralize the harmful effects of reactive oxygen species (or free radicals) with the help of trace elements functioning as a part of metalloenzymes such as glutathione peroxidase (selenium) and Cu/Zn superoxide dismutase [7] as well as enzymes for DNA integrity, protein synthesis, DNA repair, and cell proliferation. So that, growing attention is paid to the relation between trace elements and cancer. Serum and tissue levels of Cu and Zn levels were evaluated in several studies for colorectal [3], bladder [4], thyroid [5], breast [6], endometrium, and ovary [7] and oral [8] cancers.

There are also controversial data regarding the association between trace element levels and several cancers. A systematic review and meta-analysis including six studies reported that bladder cancer patients demonstrated significantly lower levels of serum Zn and markedly higher levels of serum Cu as compared with controls [4]. Similarly, Adeoti et al. [6] found higher Cu and lower Zn levels and higher Cu/Zn ratio in breast cancer patients compared with controls. Another study evaluating trace element levels in oral cancer stated that both Cu and Zn levels were higher in cancer group [8]. Dragutinovic et al. [5] also reported higher Cu and comparable Zn levels in thyroid cancer patients compared with patients with benign thyroid disease. They also reported similar Cu/Zn ratio in papillary thyroid cancer patients as compared with patients with benign thyroid disease. Recently, Khoshdel et al. [3]

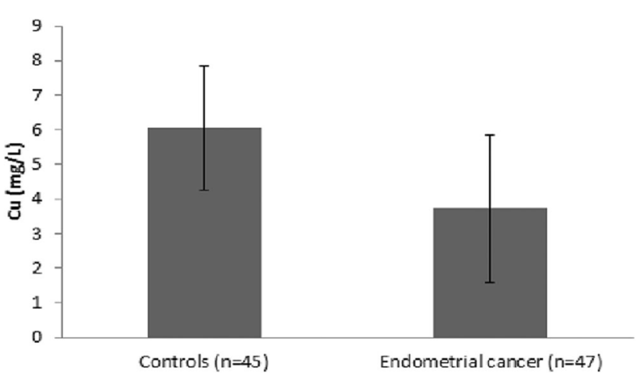

Fig. 1 Cu levels were lower in patients with endometrial cancer than controls ($p < 0.001$)

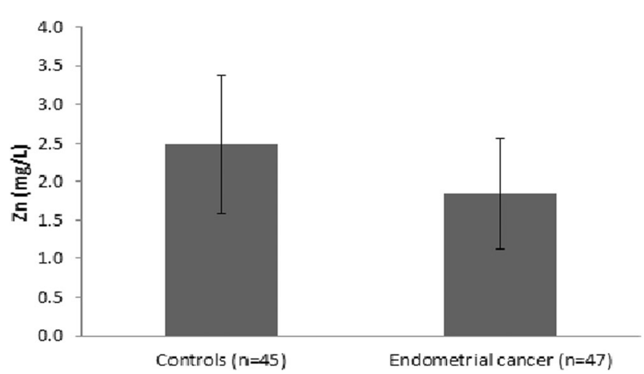

Fig. 2 Zn levels were lower in patients with endometrial cancer than controls ($p < 0.001$)

Table 2 Basic characteristics of the subjects with endometrial cancer

	n = 47
Tumor size (cm)	3.5 (0.8–7.0)
Myometrial invasion	
< 1/2	29 (61.7%)
≥ 1/2	18 (38.3%)
Stage	
1A	29 (61.7%)
1B	9 (19.1%)
2	2 (4.3%)
3A	3 (6.4%)
3B	1 (2.1%)
3C1	1 (2.1%)
3C2	1 (2.1%)
4	1 (2.1%)
Tumor grade	
1	17 (36.2%)
2	27 (57.4%)
3	3 (6.4%)
LVSI	
No	36 (76.6%)
Yes	11 (23.4%)

LVSI lymphovascular space involvement

Table 3 Correlations between Cu and Zn levels with demographic and clinical characteristics

	Cu		Zn	
	r	$p^{\dagger}$	*r*	$p^{\dagger}$
All participants	0.049	0.642	0.057	0.586
Age	− 0.016	0.882	0.152	0.147
BMI	0.097	0.359	0.175	0.096
Gravidity	0.120	0.255	0.216	*0.039*
Parity	0.049	0.642	0.057	0.586
Endometrial cancer				
Age	0.378	*0.009*	0.366	*0.011*
BMI	0.140	0.350	0.175	0.240
Gravidity	0.140	0.349	0.159	0.286
Parity	0.142	0.342	0.210	0.156
Tumor size	− 0.057	0.706	− 0.142	0.343
Stage	0.245	0.097	0.108	0.471
Grade	0.212	0.152	0.107	0.474
Controls				
Age	0.265	0.078	0.205	0.176
BMI	0.063	0.681	0.383	*0.009*
Gravidity	0.012	0.937	0.160	0.295
Parity	0.191	0.208	0.280	0.062

BMI body mass index

† Spearman's correlation test, *r* correlation coefficient

conducted a study on colorectal cancer patients. They found a significant decrease in the total mean serum Cu and Zn measurements in colorectal cancer patients as compared with the control group and concluded that imbalance of trace element levels might play an important role in colorectal cancer development. In addition, alterations in Cu and Zn tissue and serum levels were declared in lung, ovarian, prostate, testicular, and gastrointestinal cancers as well as lymphoproliferative disorders [14–19]. However, the exact role of these metals in the carcinogenic process yet has not been clearly understood.

Cu/Zn ratio and systemic oxidant load have clinical importance for aging-related degenerative diseases, nutritional status, oxidative stress, inflammation, and immune abnormalities [9–11] which may affect carcinogenesis. Mezzetti et al. [9] reported advanced age, and, particularly, advanced age-related chronic degenerative diseases are associated with a significant increase in the Cu/Zn ratio and systemic oxidative stress. Gaider et al. [10] stated that higher serum Cu and Cu/Zn ratios correlate with impairments in bone density, physical performance, and overall health in a population of elderly men with frailty characteristics. In peritoneal dialysis patients, elevated Cu/Zn ratios are found to be associated with malnutrition, increased oxidative stress, inflammation, and disrupted immune status [11]. However, our data showed lower Cu/Zn ratios in endometrial cancer group than controls despite their advanced age.

There are limited data in the literature with regard to changes in trace element levels and their relation with female reproductive system cancers. Yaman et al. [7] reported similar Cu and lower Zn tissue measurements in endometrial cancer and higher Cu and similar Zn levels in ovarian cancerous tissues. On the contrary, Nasiadek et al. [20] found similar Cu and Zn tissue levels in patients with myoma uteri and uterine cancer. Recently, Rzymski et al. [21] evaluated metal accumulation in the human uterus in connection with pathologic state and smoking habits. Their data revealed significantly increased cadmium (Cd) and lead (Pb) levels in hyperplastic and cancerous endometrial tissues, cervical intraepithelial neoplastic tissues compared with normal tissues, as well as altered status of Cu and Cu/Zn levels. Current and former smoking was found to be associated with significantly higher toxic metal accumulation as expected.

In the present study, specifically, we demonstrated that serum Cu and Zn levels in patients with endometrial cancer were significantly lower than those in control subjects as well as Cu/Zn ratio. While no significant correlation was found between Cu levels with age, BMI, gravidity, parity, and Zn levels showed a positive correlation with only parity, but not with the other parameters, when all subjects were evaluated. In addition, DM, hypertension, menopausal status, and smoking habits did not affect Cu and Zn levels. After adjustment for all confounding factors, reducing effect of the disease on Cu and Zn levels was maintained, as the measurements continued

Table 4 Cu and Zn levels with regard to demographic and clinical characteristics

	Endometrial cancer			Controls		
	n	Cu (mg/L)	Zn (mg/L)	*n*	Cu (mg/L)	Zn (mg/L)
Smoking						
No smoking	43	3.64 ± 2.19	1.76 (0.71–4.02)	38	6.14 ± 1.77	2.26 (1.23–4.54)
Smoking	4	4.57 ± 1.70	2.11 (1.77–2.47)	7	5.62 ± 1.96	2.15 (1.73–2.78)
p		0.416†	0.136‡		0.486†	0.591‡
DM						
No DM	37	3.57 ± 2.04	1.76 (0.71–2.77)	36	6.20 ± 1.76	2.24 (1.27–4.54)
DM	10	4.26 ± 2.59	2.06 (1.08–4.02)	9	5.51 ± 1.90	2.07 (1.23–3.96)
p		0.378†	0.310‡		0.303†	0.586‡
HT						
No HT	29	3.48 ± 2.07	1.65 (0.71–3.95)	30	6.01 ± 1.75	2.26 (1.23–4.36)
HT	18	4.10 ± 2.29	1.91 (1.08–4.02)	15	6.16 ± 1.92	2.07 (1.39–4.54)
p		0.344†	0.161‡		0.805†	0.923‡
Menopausal status						
Premenopausal	11	3.17 ± 2.52	1.40 (0.89–4.02)	27	5.68 ± 1.90	2.15 (1.23–4.42)
Postmenopausal	36	3.89 ± 2.04	1.79 (0.71–3.95)	18	6.63 ± 1.49	2.51 (1.44–4.54)
p		0.335†	0.217‡		0.084†	0.115‡
Myometrial invasion						
< 1/2	29	3.21 ± 1.94	1.61 (0.71–3.95)			
> 1/2	18	4.54 ± 2.28	1.77 (0.89–4.02)			
p		*0.039*†	0.347‡			
Grade						
1	17	3.01 ± 1.62	1.76 (0.71–3.95)			
2	27	3.99 ± 2.24	1.77 (0.89–3.36)			
3	3	5.30 ± 3.36	1.91 (1.28–4.02)			
p		0.143¶	0.724$			
LVSI						
Negative	36	3.45 ± 1.88	1.79 (0.71–3.95)			
Positive	11	4.60 ± 2.81	1.65 (0.89–4.02)			
p		0.225†	0.611‡			

The *p* values indicating statistically significant values were written in italics

DM diabetes mellitus, *HT* hypertension, *LVSI* lymphovascular space involvement

† Student's *t* test

‡ Mann–Whitney *U* test

¶ One-way ANOVA

$ Kruskal–Wallis test

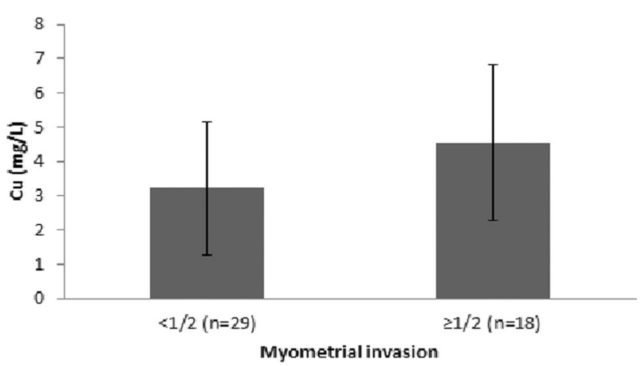

Fig. 3 In the endometrial cancer group, patients with myometrial invasion ≥ 1/2 exhibited higher Cu levels than those with myometrial invasion < 1/2 ($p = 0.039$)

to decrease in the study group independent of possible affecting factors. Subgroup analyses showed that, in endometrial cancer group, both Cu and Zn levels exhibited positive correlation with only age while no correlation was found between trace element levels and BMI, gravidity, parity tumor size, tumor grade, and disease stage. DM, HT, tumor grade, lymphovascular space involvement, and smoking habit were not effective on both Cu and Zn levels. However, in patients with myometrial invasion ≥ 1/2, Cu levels were higher than those with myometrial invasion < 1/2. Zn levels were not affected by myometrial invasion status. Our results are compatible with those of previous earlier reports showing lower measurements of serum Cu and Zn in patients with other types of

Table 5 Multivariate linear regression analysis showing the effect of endometrial cancer on Cu levels

	Regression coefficient	95% CI		*t*-statistics	*p*
		Minimum	Maximum		
Model 1					
Endometrial cancer	− 2.818	− 3.658	− 1.978	− 6.665	*< 0.001*
Age	0.072	0.027	0.117	3.154	*0.002*
Model 2					
Endometrial cancer	− 2.838	− 3.698	− 1.978	− 6.559	*< 0.001*
Age	0.071	0.025	0.117	3.079	*0.003*
BMI	0.008	− 0.059	0.076	0.248	0.805

The *p* values indicating statistically significant values were written in italics

BMI body mass index

malignant diseases such as colorectal [3], lung [14], prostate [16], and leukemia [19]. Another previous experimental rat study showed a higher incidence of carcinogen-induced colon tumorigenesis in rats with low activities of Cu antioxidant enzymes [22]. Zn deficiency has also been suggested to have adverse consequences, especially on immune functions and carcinogenesis. Christudoss et al. [23] stated in their rat study that the decrease in plasma zinc, tissue zinc, and activity of zinc-related enzymes is associated with the development of preneoplastic lesions and the biochemical parameters further decrease with progression to carcinoma. However, our data contrast with some reports of other publications that observed increased Cu and Zn levels in bladder cancer [24]. Many of the studies evaluating trace elements in several cancers reported higher Cu and lower or comparable Zn levels in cancerous patients such as breast [6], bladder [25, 26], ovary [15], thyroid [5], esophagus [27], and gastrointestinal tract [28] cancers. One previous study exhibited higher levels of both Cu and Zn in oral cancer patients [8]. Discrepant findings among the results of the published studies may be attributed to the design and sample size and the demographic and genetic characteristics of the different populations as well as the methodological differences in assessments. Interestingly, the data of the present study showed that, in the study group, both Cu and Zn levels exhibited positive correlation with only age while no correlation was found between trace element levels and BMI, gravidity, parity tumor size, tumor grade, and disease stage. DM, HT, tumor grade, lymphovascular space

Table 6 Multivariate linear regression analysis showing the effect of endometrial cancer on Zn levels

	Regression coefficient	95% CI		*t*-statistics	*p*
		Minimum	Maximum		
Model 1					
Endometrial cancer	− 0.372	− 0.529	− 0.216	− 4.725	*< 0.001*
Age	0.010	0.001	0.018	2.298	*0.024*
Model 2					
Endometrial cancer	− 0.400	− 0.558	− 0.243	− 5.063	*< 0.001*
Age	0.009	0.0003	0.017	2.064	*0.042*
BMI	0.012	− 0.001	0.024	1.898	0.061
Model 3					
Endometrial cancer	− 0.391	− 0.549	− 0.234	− 4.936	*< 0.001*
Age	0.007	− 0.002	0.016	1.562	0.122
BMI	0.011	− 0.002	0.023	1.738	0.086
Parity	0.030	− 0.021	0.082	1.172	0.245
Model 4					
Endometrial cancer	− 0.364	− 0.521	− 0.208	− 4.633	*< 0.001*
Age	0.008	− 0.001	0.017	1.687	0.095
Parity	0.036	− 0.016	0.087	1.387	0.169

The *p* values indicating statistically significant values were written in italics

BMI body mass index

Table 7 Multivariate linear regression analysis showing the effect of possible factors on Cu levels in endometrial cancer group

	Regression coefficient	95% CI		*t*-statistics	*p*
		Minimum	Maximum		
Age	0.107	0.038	0.175	3.128	*0.003*
Myometrial invasion	1.159	− 0.509	2.827	1.401	0.168
Stage	0.114	− 0.379	0.607	0.465	0.644

involvement, and smoking habit were not effective on both Cu and Zn levels. In patients with myometrial invasion ≥ 1/2, Cu levels were higher than those with myometrial invasion < 1/2. We speculate that this may be because serum Cu and Zn levels are influenced by multiple factors in serum such as inflammation and antioxidant factors. Furthermore, unbalanced dietary intake, different socioeconomic status, altered gastrointestinal absorption, alterations in the plasma metal binding protein levels, and possibly enhanced sequestration in the tumor tissues may cause inconsistent levels of serum trace elements.

To the best of our knowledge, the present study is the first in which serum trace element levels have been evaluated and a difference in Cu and Zn levels between endometrial cancer patients and controls in relation with metabolic profile and clinicopathologic features has been demonstrated. This study is also set out to correlate serum trace element levels in relation with metabolic and cardiovascular profile and clinicopathologic features of patients with endometrial cancer. Since the study was designed cross sectional, the causality could not be explained. The small sample size is a limitation. Additionally, the compared groups showed no homogeneity for some demographic characteristics such as wide age, body mass index, and menopausal status. Women with endometrial cancer are characterized by altered serum Cu and Zn levels as compared with controls. Imbalance of these trace element levels might be associated with endometrial cancer.

Actually, Cu/Zn ratio was shown to be associated with nutritional patterns, oxidative stress, and immune abnormalities; however, it was not possible to control all factors influencing Cu and Zn status such as diet and lifestyle. If copper and zinc values were examined not only in serum but also at the tissue level, clearer information might be obtained. However, with limited knowledge of the effect of trace elements on carcinogenesis, all potential functions for these elements should be evaluated for endometrial cancer including tissue accumulation and binding protein expressions in protein and mRNA level. Nevertheless, demonstration of the lower trace element levels in association with endometrial cancer suggests that these elements and related biochemical pathways merit further studies.

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Compliance with Ethical Standards

The design of the present study was approved by the Ethical Committee and Institutional Review Board of Adnan Menderes University Faculty of Medicine, where the study was conducted. Written informed consents were obtained from all participants.

Conflict of Interest The authors declare that there are no conflicts of interest.

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