

DIAGNOSTIC VALUES OF COPPER, ZINC AND COPPER/ZINC RATIO COMPARED TO HISTOPATHOLOGICAL EXAMINATION IN PATIENTS WITH BREAST TUMORS

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Abstract

Trace elements copper (Cu) and zinc (Zn) have a role in many biochemical reaction as micro source, their metabolism are profoundly altered in neoplastic diseases and since breast cancer rank the first of female cancers, this study aims to evaluate the diagnostic significance of copper/zinc ratio in 70 patients with breast tumor and compared to the grade and histopathological examination. result had been shown that there is significant difference in level of zinc and copper and copper/ zinc ratio between benign and malignant tumor and this difference persist to be present between different grade of malignant breast tumor and it had been found that copper/zinc ratio have diagnostic significance of 78.5% in discriminating between benign and malignant tissue and this had been increased to about 95.1 % in differentiating between grade of malignant breast neoplasm. So we conclude that copper/zinc ratio is higher in malignant breast tissue and could be a better indicator of grade of cancer.

Introduction

Trace elements copper (Cu) and zinc (Zn) have a role in many biochemical reaction as micro source. Copper has many physiological functions. It affects activity of many enzymes (Cu/Zn-superoxide dismutase (Cu/Zn-SOD), ceruloplasmin, cytochrome oxidase, tyrosinase, dopamine hydroxylase and lysine oxidase), both as a cofactor and as an allosteric component. These enzymes are essential for cellular respiration, defence against free radicals, melanin synthesis, formation of connective tissue and for iron metabolism. In addition, copper-dependent transcription factors play an important role in gene expression¹.

Zinc, on the other hand, present in more than 200 enzymes and transcription factors as a functional component. Therefore, zinc affects major metabolic

processes, as well as regulation of the cell cycle and cell division. The first symptom of zinc deficiency is an inhibition of cell growth and proliferation. In addition, Zn is necessary for the optimum performance of the immune system².

Copper metabolism is profoundly altered in neoplastic diseases. It has been found that raised serum copper concentration correlates with tumor incidence and burden, malignant progression, and recurrence in a variety of human cancers³⁻⁶. In contrast, Zn is found to be decreased in Gastrointestinal tract, breast and other similar cancers⁷.

Since breast cancer rank the first of the female cancer and account to 30.2 % of all cancer in Basrah south of Iraq⁸. In this study we measured the level of copper and zinc in patient with breast

tumor and try to assess the diagnostic value of copper/zinc ratio and its correlation with grade in histopathological examination in patient with malignant breast tumor.

Material and methods

The group of the study consisted of 70 patients with breast tumor aged 18–70 years recruited from the department of pathology in Al Sadder teaching hospital and 20 apparently healthy women (age matched), over a period of 1 year from June 2008–June 2009. After diagnosis, the patient were classified into benign (fibroadenoma, lactating adenoma) and malignant (invasinve ductal, intraductal carcinoma) using the histopathological examination and the mailgant tumor were graded using Scarff-Bloom-Richardson grade system into grade 1 (0 patients) grade 2(42 patients) and grade 3 (28 patient).

The blood was obtained from an antecubital vein from all the patients and control, centrifuged and serum samples without hemolysis were separated and stored at – 20 until assayed. Serum copper (Cu) and Zinc (Zn) concentration were determined by

atomic absorption spectrophotometry (Model AA – 6200, shimadzu).

The result was expressed as mean ± SD values. The mean values for zinc, copper and the Cu/Zn ratio were compared using independent t test and analysis of variance (ANOVA).between the patients group and control group and among different group of patients. The diagnostic ability of the Cu/Zn ratio was evaluated at a cutoff value of 0.50. The sensitivity and specificity, positive predictive value and negative predictive value were calculated among the histopathological diagnosis and grade of cancer.

The statistical analysis was done using SPSS software (statistical Package for the Social Sciences, version 15.0 for windows XP; SPSS, Inc, Chicago).

Results

The results of the study are presented in table I, Copper, Zinc and Cu/Zn were significantly different between the cases and controls group with higher level of copper and copper/zinc ratio in patients than in the control in contrast to lower level for zinc in patients group.

Table I: Copper, Zinc and Copper/Zinc ratio between patients and controls

	Cases (n=70)	Control (n=20)	P value*
SerumCu (µg/dl)	105.6 ± 12.8	50.6 ±12.8	<0.05
Serum Zn (µg/dl)	181.8 ± 9.8	263.6±17.9	<0.05
Cu/Zn ratio	0.80	0.19	<0.05
*p value <0.05 consider as statistically significant			

When compare patients group, we found significant difference in copper, zinc and copper/zinc ratio between those with benign and malignant breast tumors with

higher level of copper and lower level of zinc in malignant breast tumor as shown in Table II.

Table II: Copper, Zinc and Copper/Zinc ratio between benign and malignant tumor

	malignant	Benign	P value
Cu (ug/dl)	148.07 ±29.3	79.24 ± 8.1	.01
Zn(ug/dl)	131.43 ± 10.7	206.62 ± 11.9	.001
Cu/Zn ratio	1.40 ± .36	.44 ±.04	.002

* p value <0.05 consider as statistically significant

In patients with malignant breast tumor, histopathological grades classify patient into two grades 2, 3 according to their degree of differentiation. a comparison of the level of copper and zinc and copper zinc ratio between patients with grade 2 and those with grade 3 were carried out and we found significant statistical difference, in

serum zinc and copper/zinc ratio with lower value of serum zinc among poorly differentiated malignant breast tumor (grade 3), although serum copper level is also higher in poorly differentiated malignant cell but it's not reach to the degree of statistical significance as shown table III.

Table III: Copper, Zinc and Cu/Zinc between grades of malignant breast tumor

	Grade 3	Grade 2	P value
Cu (ug/dl)	174.8 ±50.7	98.4 ± 7.5	.19
Zn(ug/dl)	93.1 ± 9.7	166.3 ± 12.9	.001
Cu/Zn ratio	2.01 ± .6	.57 ±.04	.04

* p value <0.05 consider as statistically significant.

The diagnostic value of Copper/Zinc ratio at Cuttoff of >0.50, had sentivity of 78.5%, specificity of 64.3%, positive predictive value of 59.4%, negative predictive value of 81.8% compared with type of histopathological examination. By comparing it to the grade of histopathological examination, sensitivity of the copper/zinc ratio found to be 95.1% and specificity of about 71.4 %, positive predictive value of 91.3%, negative predictive value of 83.3 %.

Discussion

In this study, we found significant difference in the copper and zinc among patient with breast tumor compared with control group, and this is consistent with the study of Zowczak et al. which found increasing level of copper and decrease level of zinc in different type of tumors⁹. The level of serum copper persist to be significantly high in patients with malignant breast tumor compared with benign lesion and its consistent with the finding of K oksoy et al¹⁰. The elevation in serum Cu concentration may be due to the destruction and necrosis of the involved tissues, leading to the release of Cu into circulation¹¹. In contrast zinc level was decrease in patient with

malignant breast lesion compared with benign group. The level of zinc progressively decrease in poorly differentiated breast tumor and this is in agreement with other study which found that Zn levels in diseases with benign characteristics appears to be less than in normal, and in cases with malignancy, Zn levels drop more^{12,13}. Zinc is known to be an essential component of DNA-binding proteins with zinc fingers, as well as copper/zinc superoxide dismutase and several proteins involved in DNA repair. Thus, zinc plays an important role in transcription factor function, antioxidant defense and DNA repair¹⁴. and this could be possible explanation for great decrease in zinc level in patient with malignant breast tumor especially in poorly differentiated breast cancer.

As this study demonstrate that copper/zinc ratio is significantly different between malignant and benign breast lesion and this is consistence with finding of Y cel I, et al. state that copper/zinc ratio higher in breast cancer than control group¹⁵. With the degree of differentiation of breast cancer, this study demonstrates a higher copper/zinc ration in poorly differentiated malignant tissue (grade 3). And this finding is in

accordance with other studies who found that the Cu/Zn ratio have been found to be useful in predicting severity of cancer^{16,17}.

The sensitivity of copper/zinc ratio for diagnosis of histopathological examination type was 78.5% this was increase to 95.1% if it's compared with grade of differentiation of breast tissue. And this could be a predicator of degree of

differentiation in malignant breast tissue.

Conclusion

This study had shown significant differences among benign and malignant lesion with higher copper and lower zinc value and higher copper/zinc ratio in malignant breast lesion especially with poorly differentiated breast cancer, Copper/ zinc ratio found to be better indicator of grade of cancer.

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