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Trace elements (selenium, copper and zinc) in *de novo* acute leukemia: Serum levels and their relation with some clinical and laboratory parameters

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Abstract:

BACKGROUND: Trace elements normally appear in low concentrations in the human body and play an important role in the enzyme systems in many metabolic processes. Trace elements, mostly selenium (Se) and zinc (Zn), were involved in the defense against oxidative stress in cells. Oxidation could lead to the generation of free radicals that have been involved in the pathogenesis of many diseases, including leukemia. While Cu at the physiological level provides cellular health and at higher than the physiological level causes angiogenesis and a higher incidence of cancers.

OBJECTIVES: The aim of this study was to measure the essential trace elements (selenium, zinc, and copper) in the serum of adult patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) and their relation to some clinical and laboratory parameters.

MATERIALS AND METHODS: This case–control study comprised 39 adult patients with *de novo* acute leukemia (AL) (28 patients with AML and 11 patients with ALL) conducted from January to June 2022. The patients were collected from Iraqi Center for Hematology in Baghdad Teaching Hospital in Medical City. A total of 40 apparently healthy adults were included in this study as a control group. Peripheral blood and bone marrow smears were examined at the presentation for establishing the diagnosis. The serum level of selenium, zinc, and copper was measured by a microplate reader for both patients and the control group, before starting chemotherapy. Immunophenotyping and renal function tests (RFTs) were taken from the patient's files.

RESULTS: There was a statistically lower median level of selenium among the patients group in comparison to the control group ($P < 0.001$), while both zinc and copper did not show statistical difference between both groups ($P > 0.05$). Only hemoglobin (Hb) showed a significant negative correlation between patients with AL and the level of selenium. There was a significantly lower zinc level among the abnormal RFT group in comparison to the normal group.

CONCLUSIONS: There was a significantly lower serum selenium level in AL patients than in the control group. Selenium level showed a negative correlation with Hb among AL patients only, in which an increase in selenium level was associated with a decrease in Hb level among AL patients. There was no significant difference in the serum level of zinc and copper between AL patients and the control group. There was a significantly lower zinc level among the abnormal RFT group in comparison to the normal group.

Keywords:

Acute lymphoblastic leukemia, acute myeloid leukemia, copper, selenium, zinc

Introduction

Leukemia is a group of disorders distinguished by the accumulation of malignant white blood cells (WBCs) in the

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bone marrow (BM) and blood. Acute leukemia (AL) is classified into acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).[1,2] AML and ALL are acute hematologic malignancies characterized by abnormal differentiation and proliferation of cells of the myeloid and lymphoid lineages, respectively, resulting in the clonal proliferation of leukemic blast cells in the peripheral blood (PB), BM, and potentially extramedullary tissue.[3,4] The leukemic blast cell infiltration in the BM is accompanied by anemia and thrombocytopenia with or without neutropenia.[5] Accurate diagnosis and classification of AL are essential for treatment decisions and assessment of prognosis. Initial management requires a medical history, physical examination, complete blood count with PB smear and BM examination, immunophenotyping, cytogenetics, and molecular genetic analyses.[6] Trace elements such as selenium (Se), zinc (Zn), and copper (Cu) are inorganic micronutrients present in body fluids (micrograms per liter) and in human tissue (milligrams per kilogram).[7] Trace elements, mostly selenium (Se) and zinc (Zn), were involved in defense against oxidative stress in cells. Oxidation could lead to the generation of free radicals that have been involved in the pathogenesis of many diseases, including leukemia.[8] While Cu at the physiological level provides cellular health and at a higher than physiological level causes angiogenesis and a higher incidence of cancers.[9] Alterations in the levels of trace elements have been reported in different forms of cancer. Leukemia patients demonstrated lower levels of Zn and Se, but higher levels of Cu.[3]

Material and Methods

This case–control study comprised 39 patients with newly diagnosed AL (28 patients with AML and 11 patients with ALL) conducted from January to June 2022 and 40 apparently healthy individuals. The patients were collected from Iraqi Center for Hematology in Baghdad Teaching Hospital in Medical City. For each patient and control, verbal consent had been taken for accepting to take the PB sample. The diagnosis of AL was based on morphology and confirmed by flow cytometry and genetics on the PB and/or BMA samples. The patient and control groups were adults of both sexes. Patients with other hematological malignancies were excluded. Neither of the subject groups had taken vitamins and/or mineral supplements for at least 6 months before the study. The patients were subjected to one measurement of serum Se, Zn, and Cu before the start of the therapy. Colorimetric determination of serum Se, Zn, and Cu levels was done by a microplate reader (Promega, USA). This study was approved by review ethical committee of scientific council of pathology for Iraqi medical specializations. All patients were agree to participate in this study and written informed consent was obtained prior to study.

Statistical analysis

Most of the data were numerical and expressed as mean ± standard deviation with median and range, and according to the test of normality (Shapiro–Wilk test), the Mann–Whitney test was used for those data that were not normally distributed and unpaired *t*-test for data that are normally distributed. Some of the data were categorical and illustrated as frequency and percentage. The Pearson correlation was used to correlate between parameters within each group and expressed as (*r*), correlation coefficient, and its *P* value. $P < 0.05$ was considered the level of significance. The Statistical Package for the Social Sciences (SPSS) version 23 was used to do the statistical analysis.

Results

The mean age of AL patients was 40.44 ± 18.58 years. About 66.7% (26/39) of AL patients were male and 33.3% (13/39) were female. Of the patients group that included, there were 11 (28.2%) patients diagnosed with ALL. Out of AML patients, the most common AML type was M2, which presented in 28.2% of AL patients, followed by M5b which presented in 15.4% of patients, M3 (12.8%), M5a (7.7%), M0 (5.1%), and M4 (2.6%).

The assessment of trace elements showed that there was a statistically lower median of Se among the patients group in comparison to the control group ($P < 0.001$), while the median for Zn, Cu, and Cu/Zn ratio did not show statistical difference between both groups ($P > 0.05$) [Table 1].

The sex effect on trace elements was carried out by testing the difference between males and females of the patients

Table 1: Comparison of trace elements between the acute leukemia patients and controls

Parameter	Median (range)		*P*
	Patients (*n*=39)	Controls (*n*=40)	
Se (mmol/L)	0.14 (0.01–0.15)	0.24 (0.22–0.27)	<0.001*
Zn (µg/dL)	78.68 (68.48–100.09)	80.61 (72.76–105.08)	0.173*
Cu (µg/dL)	52.66 (12.63–116.48)	45.27 (12.7–93.47)	0.215*
Cu/Zn ratio	0.65 (0.18–1.19)	0.55 (0.14–1.16)	0.195**

*P-value by the Mann–Whitney test, **P-value by unpaired test. Se=Selenium, Zn=Zinc, Cu=Copper

Table 2: Comparison of trace elements concentration according to sex in acute leukemia patients

Parameter	Median (range)		*P*
	Male (*n*=26)	Female (*n*=13)	
Se (mmol/L)	0.14 (0.01–0.15)	0.24 (0.22–0.27)	0.918*
Zn (µg/dL)	78.82 (68.48–97.85)	78.2 (71.72–100.09)	0.918*
Cu (µg/dL)	53.22 (12.63–116.48)	52.14 (27.65–81.28)	0.941*
Cu/Zn ratio	0.65 (0.18–1.19)	0.64 (0.33–1.01)	0.977**

*P-value by the Mann–Whitney test, **P-value by unpaired test. Se=Selenium, Zn=Zinc, Cu=Copper

group for Se, Zn, Cu, and Cu/Zn; the test of difference did not demonstrate a significant difference between sex ($P > 0.05$) [Table 2].

The stratification was done based on leukemia type (AML or ALL based on flow cytometry results), and the comparison was done for trace elements and Cu/Zn ratio; no significant difference was observed [Table 3].

Furthermore, the same stratification was done based on the renal function test (RFT), and comparison was done for Se, Zn, Cu, and Cu/Zn for normal and abnormal groups; the test of difference demonstrated a significant difference between the normal and abnormal group for Zn, in which there was a significant lower Zn level among abnormal RFT group in comparison to normal group ($P < 0.05$), while no significant difference was observed for Se, Cu, and Cu/Zn ratio [Table 4].

The stratification was done based on the Nucleophosmin (NPM1) finding, and the comparison was done for Se, Zn, Cu, and Cu/Zn in the AML group. There was no significant difference between NPM1 positive (+ve) and negative (−ve) groups [Table 5].

The Pearson correlation coefficient was assessed for Se with age, WBC, hemoglobin (Hb), and platelets; only Hb showed a significant negative correlation between patients with AL and level of Se ($r = -0.3$ and $P = 0.01$), while all other variables did not demonstrate a significant correlation neither with patients group nor with the control group [Table 6].

Furthermore, the Pearson correlation coefficient for Zn with age, WBC, Hb, and platelets showed a significant negative correlation between the control group with age and zinc level ($r = -0.3$ and $P = 0.01$), while all other variables did not demonstrate a significant correlation neither with patients group nor with the control group [Table 7].

The Pearson correlation coefficient for Cu with age, WBC, Hb, and platelets did not demonstrate a significant correlation neither with the patients group nor with the control group for tested variables [Table 8].

Even, the Pearson correlation coefficient for Cu/Zn ratio with age, WBC, Hb, and platelets did not demonstrate a significant correlation neither with the patients group nor with the control group for tested variables [Table 9].

Table 3: Comparison of trace elements concentration according to acute leukemia subtypes

Parameter	Median (range)		*P*
	AML (*n*=28)	ALL (*n*=11)	
Se (mmol/L)	0.14 (0.08–0.15)	0.14 (0.01–0.15)	0.396*
Zn (µg/dL)	77.31 (68.48–90.21)	81.77 (73.09–100.09)	0.097*
Cu (µg/dL)	49.61 (12.63–81.28)	55.28 (13.19–116.48)	0.075*
Cu/Zn ratio	0.63 (0.18–1.01)	0.66 (0.18–1.19)	0.210**

*P-value by the Mann–Whitney test, **P-value by unpaired test. ALL=Acute lymphoblastic leukemia, AML=Acute myeloid leukemia, Se=Selenium, Zn=Zinc, Cu=Copper

Table 4: Comparison of trace elements concentration according to renal function tests in acute leukemia patients

Parameter	Median (range)		*P*
	Normal RFT (*n*=33)	Abnormal RFT (*n*=6)	
Se (mmol/L)	0.14 (0.01–0.15)	0.14 (0.08–0.15)	0.805*
Zn (µg/dL)	84.3 (76.86–97.85)	78.2 (68.48–100.09)	0.043*
Cu (µg/dL)	52.14 (12.63–81.28)	59.51 (41.18–116.48)	0.148*
Cu/Zn ratio	0.64 (0.18–1.01)	0.71 (0.54–1.19)	0.210**

*P-value by the Mann–Whitney test, **P-value by unpaired test. RFT=Renal function test, Se=Selenium, Zn=Zinc, Cu=Copper

Table 5: Comparison of trace elements concentration according to molecular findings in acute myeloid leukemia patients

Parameter	Median (range)		*P*
	NPM1 (positive) (*n*=33)	NPM1 (negative) (*n*=6)	
Se (mmol/L)	0.13 (0.11–0.15)	0.14 (0.08–0.15)	0.641*
Zn (µg/dL)	79.52 (75.33–85.57)	76.23 (68.48–83.67)	0.083**
Cu (µg/dL)	53.9 (39.56–64.19)	43.72 (12.63–81.28)	0.221**
Cu/Zn ratio	0.7 (0.49–0.75)	0.57 (0.18–1.01)	0.257**

*P-value by the Mann–Whitney test, **P-value by unpaired test. NPM1=Nucleophosmin, Se=Selenium, Zn=Zinc, Cu=Copper

Discussion

In this study, we found that the mean age for patients and sex were comparable to another Iraqi study.[10] However, in Western countries, the mean age for AL patients was above 65 years old.[11,12] This difference might relate to race, radiation, genetic and environmental factors, pollution, or higher and younger presentation of AL in Iraq. For sex, the majority of AL patients were male, in which it was representing 66% of the studied participants. This was in line with another study from Iraq that showed a higher percentage of males in AL patients than females.[13] In this study, AML-M2 was the most common AML subtype, while M4 was presented in one patient only. This frequency was completely different in the AML subtype from a recent publication from Iraq that showed AML-M3 was the most common AML subtype.[10,14] Such difference might relate to sessional variation for AML-M3 and the small sample size included in our analysis.

The assessment of Se showed that there was a significantly low level among AL patients in comparison to the control group. This was in line with other studies.[8,15-19] Lower levels of Se in the patients could be due to the exhaustion of the element during detoxification through glutathione

peroxidase. While Pazirandeh *et al*. did not notice any statistically significant difference in levels of serum Se between AL and healthy controls.[20] This might result from different age group as Pazirandeh et al. included only children in their work. Interestingly, Se level showed a negative correlation with Hb among AL patients only, in which an increase in Se level was associated with a decrease in Hb level among AL patients. This came in reverse with another study by Zhou *et al*. that showed serum Se level is negatively correlated with anemia risk and positively correlated with serum iron level, Hb level, and mean corpuscular Hb concentration.[21] Although the mechanisms underlying this correlation remain abstruse, the antioxidant activity of Se may play a role in these mechanisms. The regulation of oxidative stress is an important requirement for oxygen-carrying red blood cells, and deprivation of antioxidant enzymes reduces the maturity and lifespan of red blood cells.[21] While other factors, sex, RFT, type of leukemia, and NPM1 status, did not demonstrate a significant difference in Se level. Selenium or selenoproteins are required in the scavenging of free radicals, keeping redox potential, and repairing oxidized lipids. As such, there is much potential for Se to have an effect on the immune system. However, no study has yet assessed the outcome of Se supplementation on the prognosis of leukemia in the patients.

Table 6: Correlation of selenium with other hematological parameters in acute leukemia patients

Parameter	Se	
	Patients	Control
Age (years)		
r	−0.119	−0.061
P	0.471	0.709
WBC (×10⁹/L)		
r	0.067	0.079
P	0.684	0.626
Hb (g/dL)		
r	−0.389	−0.105
P	0.014	0.518
Platelets (×10⁹/L)		
r	0.081	0.058
P	0.624	0.724

WBC=White blood cell, Hb=Hemoglobin, Se=Selenium

Table 7: Correlation of zinc with other hematological parameters in acute leukemia patients

Parameter	Zn	
	Patients	Control
Age (years)		
r	−0.129	−0.388
P	0.433	0.013
WBC (×10⁹/L)		
r	0.245	−0.077
P	0.133	0.636
Hb (g/dL)		
r	0.243	−0.080
P	0.135	0.626
Platelets (×10⁹/L)		
r	0.146	0.009
P	0.374	0.957

Zn=Zinc, WBC=White blood cell, Hb=Hemoglobin

Table 8: Correlation of copper with other hematological parameters in acute leukemia patients

Parameter	Cu	
	Patients	Control
Age (years)		
r	−0.124	−0.255
P	0.453	0.112
WBC (×10⁹/L)		
r	0.298	−0.039
P	0.065	0.810
Hb (g/dL)		
r	0.216	−0.138
P	0.186	0.395
Platelets (×10⁹/L)		
r	0.042	−0.045
P	0.800	0.781

Cu=Copper, WBC=White blood cell, Hb=Hemoglobin

In this study, both Zn and Cu levels were not statistically different from the control.

The relationship between trace elements and cancer as inhibitory or causative factors has been shown in many studies.[22-24] Furthermore, another study by Valadbeigi *et al*. showed a significantly lower level of Zn among AL patients and a significantly higher level of Cu among AL patients in comparison to control groups.[15] Furthermore, Zuo *et al*. showed that serum Cu concentration was higher in leukemia patients than that in controls.[8] Most investigations of serum Cu have reported an increased Cu level in leukemia patients.[18,25,26] In contrast, a number of investigations have revealed decreased Zn in AL patients.[27-29]

Several hypotheses have been suggested to explain the lower values of Zn in this disease. Zinc is pivotal for a lot of enzymes and transcription factors that control the response to oxidative damage, DNA damage repair, DNA replication, apoptosis, and cell cycle continuation.[30] Thus, Zn deficiency may disrupt the functioning of proteins and signaling molecules required in DNA replication and repair and may upregulate the expression of a tumor suppressor protein like p53.[31] However, in our study, the result did not show a significant difference in the zinc level between AL patients and the control group. This difference between our study and other studies might come from the sample size difference included. Despite that, the accurate mechanisms through which Zn deficiency

Table 9: Correlation of copper/zinc ratio with other hematological parameters in acute leukemia patients

Parameter	Cu/Zn	
	Patients	Control
Age (years)		
r	−0.089	−0.184
P	0.589	0.255
WBC (×10^9/L)		
r	0.237	−0.029
P	0.147	0.858
Hb (g/dL)		
r	0.137	−0.116
P	0.404	0.476
Platelets (×10^9/L)		
r	0.001	−0.037
P	0.995	0.821

WBC=White blood cell, Hb=Hemoglobin, Zn=Zinc, Cu=Copper

stimulates carcinogenesis are not clear; however, convincing evidence suggests that increasing dietary or supplementary Zn not only promotes cancer prevention but can also limit established malignancies.[32]

Only lower level of Zn in AL patients associated with abnormal renal function test (P<0.05). Chronic kidney disease has been approved previously to be associated with lower Zn level and not compensated by reduced renal zinc excretion.[33] Other hematological parameters, WBC count, Hb and platelet count, sex, type of leukemia, and NPM1 status, did not demonstrate a significant difference in Zn level.

For the Cu level which was slightly higher among patients in comparison to the control and the ratio of Cu/Zn which in turn was slightly higher among patients, both of them did not demonstrate a significant difference between AL patients and the control group.

The serum Cu level is increased in leukemia, lymphomas, sarcomas, bronchogenic carcinomas, melanomas, gynecological cancers, and Hodgkin's disease.[34] Our results were in line with other studies that found that the differences between AL patients and control for Cu were not statistically significant.[10,16]

On the other hand, other investigations of serum Cu have reported an increased Cu concentration in leukemia patients, which is against our result finding.[25,26]

Copper is an essential part of Cu/Zn superoxide dismutase, a key antioxidant enzyme. In contrast, too much free Cu perturbs Zn homeostasis which, in turn, may compromise the antioxidant protection mechanism, thereby increasing oxidative stress. Finally, many articles have introduced Cu/Zn ratio as a diagnostic marker for various cancer types.[35]

In this study, no difference in Cu/Zn ratio was observed between study groups, and this might result from the nonsignificant difference in the level of both Zn and Cu between AL and the normal control group.

Other hematological parameters, WBC count, Hb and platelet count, sex, type of leukemia, RFT, and NPM1 status did not demonstrate a significant difference in Cu level and Cu/Zn ratio.

Conclusions

There was a significantly lower serum selenium level in AL patients than in the control group. Selenium level showed a negative correlation with Hb among AL patients only. There is no significant difference in the serum level of zinc and copper between AL patients and the control group. There was a significantly lower zinc level among the abnormal RFT group in comparison to the normal group.

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Conflicts of interest
There are no conflicts of interest.

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