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Effect of Chemotherapy on Zinc, Copper, Vitamin D Levels and Inflammatory Marker in Adult Acute Lymphoblastic Leukemia

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ABSTRACT

Background: In acute lymphoblastic leukemia (ALL) the bone marrow loses its ability in the differentiation and maturation of blood cells at different stages. Zinc and copper are important co-factors for several enzymes and play an important role in maintenance of DNA integrity. Changes in serum levels of zinc and copper have been found in lymphoproliferative disorders. In the present study, the aim was to compare serum levels of zinc, copper, vitamin D, and inflammatory markers after eight courses of chemotherapy. **Methods:** Participants of this study included 30 ALL patients in the age range of 15 to 65 years. A 10 mL blood sample was taken before and after eight courses of chemotherapy. The concentration of Zinc, Copper, hs-CRP, vitamin D and malondialdehyde (MDA) were measured. **Results:** There was a significant increase in serum zinc (121.7 ± 18.05 µg/dL before chemotherapy and 156.6 ± 25.00 µg/dL after chemotherapy) and a significant decrease in serum copper (661.9 ± 190.1 µg/dL before chemotherapy and 402.2 ± 93.5 µg/dL after chemotherapy) and a significant decrease in Malondialdehyde and serum vitamin D were observwd. Further, no significant differences were observed in hs-CRP after chemotherapy. **Conclusion:** Results showed that chemotherapy could decrease the burden of disease by increasing serum zinc and decreasing serum copper.

Keywords: *Acute lymphoblastic leukemia; Serum zinc and copper; Inflammation status*

Introduction

In acute lymphoblastic leukemia (ALL), the bone marrow loses its ability in differentiation and aamaturation of blood cells at different stages. ALL is a malignancy, which is characterized by clonal proliferation and accumulation of neoplastic cells (Faderl *et al.*, 1998). The disease is divided into two categories of B cell and T cell. B cell is the most common subtype in children and adults (Hoffman *et al.*, 1991).

Cancer and its treatments can affect the biological functions and change the nutritional status of patients (de Carvalho *et al.*, 2011). Zinc and copper are important cofactors for several enzymes that can

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play an important role in maintaining the integrity of DNA. Zinc and copper also act as antioxidants (Demir *et al.*, 2011) and zinc may reduce the duration and intensity of fibril neutropenia and its associated complications (Radhakrishnan *et al.*, 2013). Changes in serum levels of zinc and copper have been found in lymphoproliferative disorders in addition to the breast cancer, lung, and gastrointestinal tumors (Avisar *et al.*, 2012, Shils and Shike, 2006). Experimental data support the presence of slight zinc deficiency in malignancies (Sgarbieri *et al.*, 2006). Zinc deficiency may cause disturbances in oxidation, mitochondrial function, DNA repair, and cancer induction and progression. Impaired zinc metabolism in pathogenesis of leukemia was identified in 1949. Zinc seems to improve the overall ability of patients in resisting the toxic side effects of chemotherapy (Zuo *et al.*, 2006).

Copper is a necessary element for various metalloenzymes including ceruloplasmin, cytochrome oxidase, and dopamine hydroxylase. In normal conditions, 96% of serum copper is in the ceruloplasmin. Ceruloplasmin is a serum glycoprotein with 8 copper atoms and 12 sialic acid chains per molecule, required for oxidation of Fe^{+2} to Fe^{+3} for storage in the form of ferritin or being transmitted via transferrin. If catabolism of ceruloplasmin depends on cutting two sialic acids by neuraminidase, any phenomenon that reacylates the cut points, inhibits the catabolism of ceruloplasmin. Thus, the increase of serum copper observed in malignancies is due to the reduction of ceruloplasmin's catabolism. Another speculation is that the balance between serum sialic acid and ceruloplasmin is due to reduced activity of neuraminidase or increased concentration of sialic acid. This increase of acylation or decrease of deacylation occurs in the liver (Fisher and Shifrine, 1978). In cancer, we have oxidative conditions in body that can cause oxidative damage to lipids and production of malondialdehyde (MDA). MDA is a mutagenic compound in mammalian cells and can have reaction with DNA bases such as guanine (G), adenine (A), cytosine (C), and resulted in the production of M1G (Malodialdehyde deoxy Guanosin) M1A (Malodialdehyde deoxy Adenine), and M1C (Malodialdehyde deoxyCitosine), which can cause damage to DNA (Valko *et al.*, 2006). Studies showed that hs-CRP level is positively associated with cancer and in the recent studies there was a positive relation between elevated hs-CRP and risk of incident of any type of cancer. There are two hypotheses about increasing hs-CRP in cancer; the first one is that, increasing in hs-CRP level is a result of underlying cancer and the second believes that because of oxidative stress in cancer, inflammation can initiate carcinogenesis by inactivating mutations in tumor-suppressor genes or post translational modifications in proteins involved in DNA repair or apoptosis control (Lee *et al.*, 2011). To our knowledge, there are not any data about evaluating serum levels of vitamin D in these patients before and after chemotherapy.

In the present study, the aim was to compare serum levels of zinc, copper, vitamin D, and inflammatory status after eight courses of chemotherapy.

Materials and Methods

Study design and participants: In this before and after study, After confirmation of the Ethics Committee of Tehran University of Medical Sciences, during two years (2014-2016), 30 patients (17 men and 13 women) with ALL, who referred to Taleghani hospital participated in this study (leukemia was diagnosed through bone marrow aspiration and the cells were classified according to the French-American-British). Chemotherapy was done based on HYPERCVAD protocol for these patients.

In the first visit of patient for chemotherapy, 10 mL of venous blood was taken prior to treatment. Blood samples were then centrifuged for 20 minutes at 400 g. At the end, the plasma was transferred to another tube. All samples were stored at -80°C. Taking blood samples were repeated at the end of the eighth chemotherapy courses.

*Measurements***:** Serum concentration of zinc was measured by ZellBio GmBh (V4126) kit that is made by Germany and (nm 546 calorimeter)

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based on the directions of kit producer corporation. The human prospective value is usually 72.6-127 µg/dL (11.1-19.5 µmol⁄L) for men and 70-114 µg/dL (10.7-17.5 µmol/L) for women, with the sensitivity of 10 µg⁄dL.

Serum copper was measured by ZellBio GmBh (V4126) kit that is made by Germany and (nm 5u0-590 calorimeter) based on the directions of kit producer corporation. This kit could measure copper in serum in the range of 70-140 µg/dL (11-22 µmol⁄L) for men and 80-155 µg/dL (12.6-24.4 µmol⁄L) for women, with the sensitivity of 1 µg⁄dL.

Vitamin D was measured by Calbiotech (cat. No: VD220B) kit that is made by Canda, based on ELISA method, according to the directions of kit producer corporation. According to this kit, values of vitamin D were defined as bellow: <10 ng/mL deficient, 10-30 ng/mL inadequate, 30-100 ng/mL adequate, and >100 ng/mL toxic. The sensitivity of this kit was 67.0 ng⁄mL.

hs-CRP was measured by Canadian DBC (diagnostics Biochem Canada) kit (cat. No: CAN-CRP-4360) based on ELISA method and following the directions of kit producer corporation. This kit could measure hs-CRP 132-9710 ng/mL for men and 139-6578 ng/mL for women with a sensitivity of 10 ng/mL.

ZellBio GmB, (CAT No.ZB-MDA96A), performed measurement of serum MDA (CAT No.ZB-MDA 48A) that are made by Germany via calorimeter and according to the manufacture's user guide. This kit was created by using a combination of MDA-TBA formed by the reaction of MDA and thiobarbituric acid (TBA) under a high temperature operation. This kit was capable of measuring MDA in the range of 0.78-50 µM and its sensitivity was 0.1 µM.

Data analysis: In this study, data were analyzed using SPSS version 12. At first, data distribution was checked by Kolmogorov-Smirnov test; in the case of normal distribution, paired samples t-test was used to compare the means before and after chemotherapy, and if the distribution of the data was not normal, Wilcoxon test was applied to compare before and after means. In addition, p-value < 0.05 was considered statistically significant.

Ethical considerations: Tehran University of Medical Sciences ethic committee approved this study.

Results

The mean of hematological variable before and after of chemotherapy are summarized in Table 1. Results showed that the serum concentration of zinc at the end of 8th chemotherapy course raised significantly and serum copper decreased significantly in these patients. In addition, our result showed significant decrease in serum concentration of MDA and vitamin D at the end of eight course of chemotherapy, whereas serum concentration of hs-CRP showed no significant difference. Our result showed that before chemotherapy 63.3% of ALL patients had insufficient serum vitamin D whereas all the patients had insufficient serum vitamin D after 8th course of chemotherapy.

Table 1. Mean ± SD of serum concentration of hematological variables in ALL patients before and after chemotherapy

Variables	Before	After	P-value[a]
Zinc (µg/dL)	121.7 ± 18.0	156.6 ± 25.0	< 0.001
Copper (µg/dL)	661.9 ± 190.1	402.2 ± 93.5	< 0.001
Malondialdehyde (µM)	19.0 ± 2.67	12.9 ± 3.6	< 0.001
hs-CRP (ng/mL)	9667.9 ± 2472	9773.2 ± 1556.3	0.8612
Vitamin D (ng/mL)	21.8 ± 12.9	13.5 ± 2.2	0.0136

[a]: Wilcoxon test

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Discussion

The desirable levels of trace elements are needed for many physiological and metabolic functions (de Carvalho *et al.*, 2011). Results of this study on serum zinc and copper agree with those of two other studies (Demir *et al.*, 2011, Zuo *et al.*, 2006) in which the serum level of zinc was significantly lower and serum level of copper was significantly higher in patients at the time of diagnosis compared with healthy people. In another study, serum level of copper was significantly higher in patients than in healthy people at the time of diagnosis and its level decreased after starting the treatment. However, in this study, the concentration of serum zinc was the same in patients and healthy individuals. This study also found no correlation between oral intake of zinc, copper, and their serum concentrations (Sgarbieri *et al.*, 2006). Results of another study showed that serum zinc concentrations were similar in patients with ALL and healthy individuals (Radhakrishnan *et al.*, 2013). Results of another study on patients with lymphoblastic leukemia showed a significant increase in serum concentration of copper and a significant reduction in cell zinc compared to healthy controls (Carpentieri *et al.*, 1986).

Our data showed that serum zinc increased after eight courses of chemotherapy, meanwhile serum copper decreased. The zinc deficiency at the onset of diagnosis can be due to reduced oral intake, anorexia, recurring infections, or excretion through urine and sweat (Beguin *et al.*, 1987); increased zinc and decreased copper serum in the second stage can occur because of reducing the burden of disease due to chemotherapy. In the case of zinc, increase of oral intake is also likely to be effective. Oral intake of zinc was evaluated in these patients and our data were published in another article.

The significant reduction of vitamin D in the second stage of this study, after the completion of the disease can be due to the long-term hospitalization of the patients. In addition, according to ALL patients, they rarely went out because they were worried of catching infectious, bacterial, and viral diseases because of their weak immune systems after chemotherapy, fatigue, or weakness; they only went out to go to the hospital.

A study on children with ALL, reported significant reductions in serum levels of their total antioxidant capacity (TAC), the mean of serum MDA concentration, and plasma concentration of vitamin C compared to the control group (Beguin *et al.*, 1987). In the present study, the serum level of hs-CRP was excessively higher than the normal range, although hs-CRP changes showed no significant difference before and after treatment. The fact that hs-CRP did not change significantly in this study was probably because it takes more time after chemotherapy for inflammatory markers to decrease. Moreover, factors we did not control in this study, such as smoking can also affect hs-CRP level.

Our data showed significant decrease in serum MDA at the end of the study. Lymphocyte cells are the source of producing superoxide anion and other oxygen metabolites (Mehde and Yousif, 2014). After starting chemotherapy and recovery from the disease, leukemic cells' burden decreases and as a result, serum MDA decreased at the end of treatment.

According to the findings of this study, administration of vitamin D supplementation regarding RDA is recommended in patients with ALL for improving their antioxidant levels and response to the treatment. It seems essential to offer nutritional education for these patients in order to improve their nutritional status during chemotherapy, reduce its side effects, and improve their response to the therapy.

To the best of our knowledge, no study has been conducted so far in Iran for measuring blood biochemical parameters in adults suffering from ALL. Only two studies have been conducted in this domain; one of them was on serum vitamin C and TAC concentrations in children with ALL, and the other investigated serum copper concentration at the onset of diagnosis. In most studies, parameters were

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measured only in the beginning of the diagnosis. However, in this study, assessment of biochemical parameters in these patients provided more accurate information about the effects of chemotherapy on patients' status before and after chemotherapy.

In addition, due to time and budget constraints, only the first grade inflammatory markers were measured. Measuring the second grade inflammatory markers in further studies may provide a better interpretation of findings.

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Authors' contributions

Vafa M (as a corresponding author), Djafarian K designed research. Rezvani H confirmed ALL disease and helping to design some parts of the study. Azargashb E analyzed data Akhgar C conducted research and wrote the paper. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest regarding the publication of this paper.

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