Am J Blood Res 2018;8(3):21-28
www.AJBlood.us /ISSN:2160-1992/AJBR0083498

Original Article

Comparing serum levels of zinc, copper, certain antioxidant vitamins and dietary intakes in acute lymphoblastic leukemia (ALL) patients before and after chemotherapy

Camellia Akhgarjand[1], Kurosh Djafarian[1], Hamid Rezvani[2], Eznollah Azargashb[3], Mohammadreza Vafa[4]

[1]Department of Clinical Nutrition and Dietetics Therapy, School of Nutrition Sciences and Food Technology, Tehran University of Medical Sciences, Tehran, Iran; [2]Hemato-Oncology Ward, Taleghani Hospital, Shahid Behshti Medical Sciences University, Tehran, Iran; [3]Department of Community Medicine, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [4]Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

Received August 3, 2018; Accepted August 29, 2018; Epub October 5, 2018; Published October 15, 2018

Abstract: Acute lymphoblastic leukemia (ALL) is a malignant hematologic disease. Cancer and its treatments can affect biological functions and change the nutritional status of patients. Zinc and copper are important cofactors for several enzymes and play an important role in maintaining the integrity of DNA. In ALL, we have oxidative conditions in the body that can cause oxidative damage to lipids and the production of malondialdehyde (MDA). So that the aim of this study is comparing serum levels of copper, zinc and inflammation before and after chemotherapy. Thirty ALL patients between 15 to 65 years old participated in this study. A blood sample of 10 cc was taken before and after eight course of chemotherapy. We observed a significant increase in serum zinc as well as a significant decrease in serum copper, vitamin D and Malondialdehyde. We have not seen any significant differences in hs-CRP after chemotherapy. These changes might be due to chemotherapy and changing lifestyle of patients toward healthy eating nutrition and serum vitamin D get worse and because of sedentary life style in these patients there is an essential need to anthropometric measurements during treatment.

Keywords: Precursor cell lymphoblastic leukemia-lymphoma, serum zinc and copper, antioxidant status, body composition

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant hematologic disease which is characterized by the accumulation of lymphoblast [1]. In this disease, the bone marrow loses its ability in the differentiation and maturation of blood cells at different stages [2]. In early 1990, ALL was an incurable disease, but the chance of overall survival has since improved by 30-40%. The disease is divided into two categories of B cell and T cell. B cell is the most common subtype in children and adults [1]. The desirable levels of trace elements are needed for many physiological and metabolic functions [3]. Changes in serum levels of zinc and copper have been found in lymph proliferative disorders in addition to breast cancer and lung and gastrointestinal tumors [4, 5].

A number of studies have shown that there is a correlation between zinc deficiency and cancer progression; also, experimental data support the presence of slight zinc deficiency in malignancies [6]. Zinc deficiency may cause disturbances in oxidation, mitochondrial function, DNA repair, and cancer induction and progression. Impaired zinc metabolism in the pathogenesis of leukemia was identified in 1949. Zinc seems to improve the overall ability of the patients in resisting the toxic side effects of chemotherapy [7]. There is no doubt that exposure to large amounts of copper creates the potential of damage to human cells and their components, especially through the production of ROS. Copper binds to DNA in cells (DNA's tendency towards copper ions is higher than towards other necessary metal ions) and causes impairment of chromosome folding and

leads to the disruption in the integrity of chromosome building. Moreover, it causes oxidative damage to DNA and chromatin, break in DNA strands, point mutations, and chromosome instability [8].

Reactive oxygen species (ROS) plays a dual role in biological systems. Its consists of beneficial effects including defense against infectious agents, and participates in a number of cellular signaling pathways; however, in high concentrations, ROS can damage the structure of cells such as fats, membranes, proteins, and nucleic acids. The deleterious effects of ROS can be balanced by enzymatic and non-enzymatic antioxidants [9]. In cancer, we have oxidative conditions in the body that can cause oxidative damage to lipids and the production of malondialdehyde (MDA). MDA is a mutagenic compound in mammalian cells, bacteria, and carcinogen component in mice. MDAs can react with DNA bases such as guanine (G), adenine (A), and cytosine (C) and result in the production of M1G, M1A, and M1C, which can cause damage to DNA. Superoxide Dismutase (SOD) is one of the most efficient antioxidant enzymes that converts superoxide anion into O_2 and H_2O_2 [2]. Thus, aim of this study was to investigate serum zinc, copper and enzymatic and non-enzymatic antioxidants before and after chemotherapy in patients with ALL.

Material and methods

This study is a before and after interventional 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). Noteworthy that there was a consent form for every participant which has been signed by her/him and also they had been informed they could leave the study whenever they want. In the first visit of patient for chemotherapy and at the end of eight course of chemotherapy, 10 mL of venous blood was taken prior to treatment then heparinized blood samples were centrifuged for 20 minutes at 400 g. At the end, the plasma was transferred to another tube. All samples were stored at -80°C. The weight of each patient was measured with light clothing, using a leveraged e-body scale (OMRON BF511) which accuracy was 100 gr. For weight measurement, patients stood with their knees and back straight and look straight ahead, the arms were horizontally raised and the elbows are extended straight at a 90 angle, then after the number fixed, it was recorded. Meanwhile we ensured that patients were without edema. Furthermore, height without shoes was measured by a meter mounted on the wall with an accuracy of 0.5 cm. Also, each patient's body composition, fat percentage, and lean body mass were measured using e-body scale, and then, information about each person was recorded in the questionnaire. Taking blood samples, weighing, and measuring body composition were repeated at the end of the eighth chemotherapy courses. To determine the dietary intakes of patients, before the first and last courses of chemotherapy, 24-hour recall in 2 days was used for measuring of zinc, copper, vitamins C and E. The nutritional software Nutrition IV was used for analysis of dietary intake.

In this study, data were analyzed using SPSS Ver12. At first, data distribution was checked by Kolmogorov-Smirnov test; if the data had a 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 used for comparing before and after means. $P < 0{\cdot}05$ was considered statistically significant.

Laboratory measurements

MDA: Measurement of serum malondialdehyde was performed by ZellBio GmbH (CAT No. ZB-MDA96A), (CAT No.ZB-MDA 48A) via colorimetric, 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 malondialdehyde in the range of 0.78-50 μM, and its sensitivity was 0.1 μM.

SOD: SOD was calculated by ZellBio GmbH (CAT No. ZB-SOD96A, V407 (CAT No. ZB-SOD48A, V407) kit and (nm 420 calorimeter) following the directions of kit producer corporation. This kit used anion superoxide to hydrogen peroxide and oxygen chemical reaction transformation. This test could measure superoxide dismutase

Table 1. Mean and standard deviation of serum concentration of Cu, Zn, Zn-Cu SOD in ALL patients before and after chemotherapy

Biomarker	Before chemotherapy		After chemotherapy	
	Mean	SD	Mean	SD
Zn (μg/dl)	121.7	18.05	156.6[a]	25
Cu (μg/dl)	661.9	190.1	402.2[b]	93.5
Zn-Cu SOD (U/ml)	75.2	6.5	113.9[c]	4.9

a, b, c < 0.0001

Table 2. Antioxidants' vitamins activity in ALL patients before and after chemotherapy

Biomarker	Before chemotherapy		After chemotherapy	
	Mean	SD	Mean	SD
Vitamin C (μg/ml)	1.9	0.45	1.68	0.69
Vitamin E (μg/ml)	7.17	2.5	10.2*	4.2
Vitamin D (ng/ml)	21.8	12.9	13.5▲	2.2
TAC (U/ml)	12.9	3.69	15.7■	3.46

*P=0.0005; ▲P=0.0136; ■P < 0.0001.

in the range of 5-100 U/mL, with 1 U/mL sensitivity. (The activity unit of superoxide dismutase is considered to be the quantity of sample which can catalyze 1 μm anion superoxide to oxygen and hydrogen peroxide).

Serum zic: Serum concentration of zinc was measured by ZellBio GmbH (V4126) kit and (nm 546 calorimeter) based on the directions of kit producer corporation. The human prospective values 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 vitamin E: Serum concentration of vitamin E was measured by ZellBio (CAT# ZB-VIT-9648A, V402) kit and (nm 536 calorimeter) according to the directions of kit Producer Corporation. This kit could measure vitamin E in the range of 20-25.1 (μg)/ml with 0.3 (μg)/ml sensitivity.

Serum vitamin C: Serum concentration of vitamin C was measured by ZellBio (ZB-VITC-4896A) (V407) kit and (nm 520 calorimeter) according to the directions of kit producer corporation. This kit could measure vitamin C up to 20 (μg)/ml with 1.0 (μg)/ml sensitivity.

Srum copper: Serum copper measurement was carried out by ZellBio GmbH (V4126) kit 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 0.1 (μg)/dl.

Serum TCA: TAC was measured by ZellBio GmbH (cat. No: ZB-TAC-A96), (cat. No: ZB_TAC-A48) kit and (resuscitation oxidation calorimeter) according to the directions of kit producer corporation. This kit could measure TAC between 0.125-2 mM (125-2000 μmol/L) with 1.0 mM sensitivity.

Serum vitamin D: Vitamin D was measured by Calbiotech (cat. No: VD220B) kit, 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: hs-CRP measurement was carried out by Canadian DBC kit (cat. No: CAN-CRP-4360), based on ELISA method, following the directions of kit producer corporation. This kit could measure hs-CRP 132-9710 ng/ml for men, and 139-657 ng/ml for women, with the sensitivity of 10 ng/ml.

Results

In our study 43.3% of participants were female and 56.6% were male. The data of essential trace elements and superoxide dismutase are summarized in **Table 1**. Results showed that the serum concentration of zinc and Zn-Cu SOD at the end of 8th chemotherapy course raised significantly and serum copper decreased significantly in these patients (**Table 1**). The data of antioxidant vitamins showed that at the end of chemotherapy period, the serum concentration of vitamin D decreased significantly, whereas the serum concentration of vitamin E and TAC increased significantly, and the serum concentration of vitamin C showed no significant difference (**Table 2**). Our result showed significant decrease in serum concentration of MDA at the end of eight course of chemotherapy (**Figure 1**), whereas serum concentration of hs-CRP showed no significant difference (**Figure**

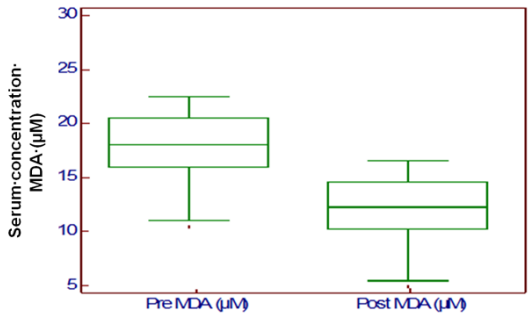

Figure 1. Serum concentration of MDA before and after chemotherapy in ALL patients (P < 0.0001).

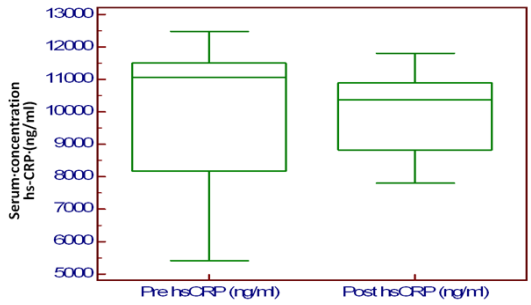

Figure 2. Serum concentration of hs-CRP before and after chemotherapy in ALL patients (P=0.8612).

2). The data of dietary intake showed that at the end of the study, dietary intake of zinc, copper, vitamin C and vitamin E increased significantly (**Table 3**). The data of body composition showed significant decrease in weight, BMI and fat free mass (FFM) at the end of eight course of chemotherapy, whereas fat mass increased significantly (**Table 4**).

We adjusted the effect of dietary intake with ANCOVA test. Results showed that, with dietary intake Covariance the results didn't any changes. It shows that chemotherapy independently could change the serum levels of Zinc, Copper and Vitamin C and Fat Free Mass (FFM).

Discussion

Just as other chronic diseases, cancer can have adverse effects on the nutritional balance because this disease and its treatment may cause anorexia, nausea, indigestion, and consequently reduction in the uptake of nutrients [10]. Results of this study about serum zinc and copper are agree with those of two other studies [6, 11]. 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 the patients and healthy individuals. This study also found that there is no correlation between oral intake of zinc and copper, and their serum concentrations [10]. Results of another study showed that serum zinc concentrations were similar in patients with ALL and healthy individuals [12]. 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 [13].

Our data showed that after eight course of chemotherapy serum zinc and dietary intake of zinc increased and despite of reduction in serum copper, dietary intake of copper increased. Since serum concentration of zinc is sensitive to oral intake [13] the zinc deficiency at the onset of diagnosis can be due to burden of the disease, reduced oral intake, anorexia, recurring infections, or excretion through urine and sweat [14]; increased zinc and decreased copper serum in the second stage can occur because of reducing the burden of disease due to chemotherapy. In case of zinc, increase of oral intake is also likely to be effective.

One reason for the significant increase in oral intake of copper and zinc could be that, based on our observations, with the onset of disease, the dietary pattern of the patients becomes healthier, and the intake of nutrients such as nuts, fish, poultry, and dried fruits which are rich in zinc and copper increases (since patients do not usually consume raw fruits because of neutropenia and the increased likelihood of infection after chemotherapy). Despite a significant increase in copper's oral intake, a significant reduction in its serum concentration was observed in the second stage, because the serum copper concentrations are kept constant not only in the blood but also in different organs, indicating the presence of powerful mechanisms in copper homeostasis, unless a disease alters it [8], for instance in the present study in which leukemia changed serum copper levels in the patients. Note that, chemotherapy

Table 3. Mean and standard deviation of dietary intake of zinc, copper, vitamin C and vitamin

Biomarker	Before chemotherapy		After chemotherapy		*P* value
	Mean	SD	Mean	SD	
Zinc (mg)	2.7	1.5	3.9	1.6	0.0092
Copper (mg)	7.17	2.5	10.2	4.2	< 0.0001
Vitamin C (mg)	21.8	12.9	13.5	2.2	< 0.0001
Vitamin E (mg)	12.9	3.69	15.7	3.46	< 0.0001

Table 4. Mean and standard deviation of body composition in ALL patients before and after chemotherapy

Biomarker	Before chemotherapy		After chemotherapy	
	Mean	SD	Mean	SD
Weight (Kg)	66.1	10.5	58.8[a]	9.1
BMI (Kg/m^2)	24	1.6	21.6[b]	1.4
Fat mass (%)	16.8	1.7	20.4[c]	2.4
FFM (%)	27.4	1.8	18.4[d]	4.4

a, b, c, d < 0.0001.

independently from dietary intake could change the serum levels of zinc and copper. In this study, a significant increase of anti-inflammatory and antioxidant vitamins (except for vitamin C) and malondialdehyde and antioxidants indicators was observed in the patients with acute lymphoblastic leukemia before and after treatment. Nevertheless, there was no significant difference in hs-CRP before and after treatment.

A study on children with ALL reported significant reductions in serum levels of their total antioxidant capacity (TAC), the mean of serum malondialdehyde concentration, and plasma concentration of vitamin C compared to the control group [15]. In another study on children with solid tumors and ALL, results showed a significant decrease of antioxidant capacity in patients compared with the control group. In addition, antioxidant capacity was significantly lower in patients with ALL [16]. Findings of a study on children with ALL at the time of the first diagnosis, and then 3 and 6 months after the start of treatment indicated a significant reduction in total serum antioxidants in the aqueous phase (uric acid, vitamin C, and other items such as flavonoids), significant increased plasma concentration of vitamin C in the first three months, and a significant reduction of its concentration in the second three months. However, the concentration of serum vitamin E did not change significantly [17].

Lymphocyte cells are the source of producing superoxide anion and other oxygen metabolites [15]. In addition, production of superoxide by polymorph nuclear leukocytes increases significantly in leukemia patients, especially the patients with acute lymphoid or non-lymphoblastic leukemia [18]. Accordingly, at the beginning of treatment, antioxidant enzymatic (Cu-Zn SOD) and non-enzymatic defense (vitamin E) and total antioxidant capacity (TAC) are low; after starting chemotherapy and recovery from the disease, leukemic cells' burden decreases as a result of which oxidative stress and the amounts of these parameters increases.

Vitamin C reduction can occur because the leukemic cells' tendency to multiply is inhibited through highly viscous intracellular glycosaminoglycans; in order to produce this substance, the cells need to release hyaluronidase enzyme for producing which vitamin C is used [16]; thus, consumption of vitamin C in malignant blood cells reflects an adaptive physiological response [19].

C reactive protein (CRP) is an acute phase protein, increased in bacterial infections, inflammatory diseases, trauma, surgery, and cancer. CRP is produced in the liver in response to the increased levels of cytokines after inflammation. Increased CRP levels in cancer can occur for the following reasons: tumor growth can cause inflammation and increased plasma levels of CRP; moreover, tumor cells can produce various types of cytokines and chemokine, and these factors lead to the secretion of interleukin-6 and stimulation of the liver for CRP production; finally, CRP is probably a part of the host's immune response to the tumor. Studies have shown that increased levels of CRP are associated with early death after cancer diagnosis [20].

In the present study, the serum level of CRP was excessively higher than the normal range, although CRP changes showed no significant difference before and after treatment. The fact that hs-CRP did not change significantly before

and after treatment in this study was probably because it takes more time after chemotherapy for inflammatory markers to decrease. Moreover, factors we did not control for in this study, such as smoking, can also affect the levels of hs-CRP. Thus, more studies are needed in this area.

The significant reduction in 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 of fear of catching infectious, bacterial, and viral diseases because of their weak immune systems after chemotherapy, fatigue, or weakness, and they only went out to go to the hospital.

Poor nutritional status which is shown through body composition is an important concern for the patients with cancer. Nutritional status is associated with decreased tolerance of chemotherapy, increased susceptibility to infection, and poor clinical results. Nutritional problems are different based on the type of cancer and its treatment, and may be a concern at the time of diagnosis, during treatment, and in post-treatment years [21]. Our investigations of acute lymphoblastic leukemia in the patients before and after treatment showed significant increases in weight, body mass index (BMI), and fat mass index (FMI), and significant decreases in body fat mass percentage.

Studies on children with leukemia demonstrated increases in their BMI and FMI compared to the control group 1-2 years after treatment [22]; increased percentage of body fat mass from 24% at the time of diagnosis to 28% at completion of treatment [23]; increased weight and fat mass and decreased muscle mass during the 12-month treatment of the children under two different treatment protocols (chemotherapy and chemotherapy plus radiation to the skull [25]; increased fat mass percentage and decreased physical activity in children after 2.2 years after treatment (first evaluation) and smaller increase of fat mass percentage in the patients compared to the control group in the second evaluation (one year after the first) [24].

In this study, the significant decrease in fat free mass (FFM) percentage and the significant increase of fat mass in the second stage (after the completion of treatment) may have occurred due to the effects of chemotherapeutic agents. Corticosteroids are associated with muscle weakness, myopathy, and muscle mass loss [23]. In addition, decreased physical activity and reluctance to have it because of increased fatigue can be another reason for this problem [25]. Weight loss and consequently reduction in BMI in these patients may have occurred because, as noted above and as in other chronic diseases, cancer can have adverse effects on the nutritional balance of the patients, since this disease and its treatment may cause anorexia, nausea, indigestion, and consequently reduction of nutrient intake [10]. Findings of this study showed that although weight and body mass decreased in these patients, body fat percentage increases. Thus, chemotherapy not only led to weight loss, but also changed body composition, and therefore we need a more serious pursuit of nutritional demands.

We concluded that in patients with acute lymphoblastic leukemia, serum zinc and copper concentrations increased and decreased, respectively, after completion of chemotherapy. In these patients, the concentrations of antioxidant and anti-inflammatory vitamins (vitamins E and D) increased, but serum concentrations of vitamin C showed no significant change; antioxidant indices (TAC and a Cu-Zn SOD) also increased. In these patients, after completion of chemotherapy, inflammatory marker of MDA decreased, wile, the serum concentration of hs-CRP did not significantly change; body weight, BMI and FFM decreased, whereas body fat mass increased.

According to the findings of this study, administration of antioxidant supplements (especially vitamin D) regarding RDA is recommended in patients with acute lymphoblastic leukemia for improving their antioxidant levels and response to the treatment. Moreover, since the consumption of vitamin C is high (due to the high tendency for its intake in leukemic cells), these patients may need higher doses of vitamin C compared to healthy people. 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. Considering the effects of chemotherapy on the composition of body, it seems necessary that these patients be offered occupational therapy, rehabilitation, and proper exercises to maintain muscle mass during treatment.

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

In most studies, parameters were measured only in the beginning of the diagnosis. However, in this study, assessment of biochemical and anthropometric parameters in these patients indicated more accurate information about the effects of chemotherapy on their nutritional and anthropometric status before and after chemotherapy, providing the treatment team with solutions for the improvement of nutritional status and responses to treatment.

In this study, the use of cigarettes and drugs (for pain relief) were observed in some patients. Thus, it is necessary to use a questionnaire to assess lifestyles and factors such as smoking and drug use in the patients and their impacts on the treatment procedure. In addition, due to time and budget constraints, only the first grade inflammatory markers were measured. Measuring second grade inflammatory markers in further studies may provide a better interpretation of findings. In order to measure body composition, e-body scale was used due to budget constraints. Since this study considered the changes of body composition, using this scale has not compromised the results.

Acknowledgements

We thank all the staff of Taleghani hospital and biochemical laboratory. This study was part of a Master's thesis of Nutritional Science, funded by the Vice-president of Research in Tehran University of Medical Sciences (Grant 161-02-9326405).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Mohammadreza Vafa, Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Shahid Hemmat Highway, Tehran, Iran. Tel: 0912-5332628; E-mail: rezavafa@yahoo.com

References

[1] Hoffman R, Benz Jr EJ, Silberstein LE, Heslop H, Anastasi J and Weitz J. Hematology: basic principles and practice. Elsevier Health Sciences, 2013.

[2] Battisti V, Maders LD, Bagatini MD, Santos KF, Spanevello RM, Maldonado PA, Brulé AO, do Carmo Araújo M, Schetinger MR and Morsch VM. Measurement of oxidative stress and antioxidant status in acute lymphoblastic leukemia patients. Clin Biochem 2008; 41: 511-518.

[3] de Carvalho G, Camilo ME and Ravasco P. What is the relevance of nutrition in oncology? Acta Méd Port 2011; 24 Suppl 4: 1041-1050.

[4] Avisar A, River Y, Schiff E, Bar-Sela G, Steiner M and Ben-Arye E. Chemotherapy-related cognitive impairment: does integrating complementary medicine have something to add? Review of the literature. Breast Cancer Res Treat 2012; 136: 1-7.

[5] Shils ME and Shike M. Modern nutrition in health and disease. Lippincott Williams & Wilkins, 2006.

[6] Demir C, Demir H, Esen R, Sehitogullari A, Atmaca M and Alay M. Altered serum levels of elements in acute leukemia cases in Turkey. Asian Pac J Cancer Prev 2011; 12: 3471-3474.

[7] Wysokinski D, Blasiak J and Wozniak K. Zinc differentially modulates DNA damage induced by anthracyclines in normal and cancer cells. Exp Oncol 2012; 34: 327-331.

[8] Linder MC. The relationship of copper to DNA damage and damage prevention in humans. Mutat Res 2012; 733: 83-91.

[9] Valko M, Rhodes C, Moncol J, Izakovic M and Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact 2006; 160: 1-40.

[10] Sgarbieri UR, Fisberg M, Tone LG and Latorre Mdo R. Nutritional assessment and serum zinc and copper concentration among children with acute lymphocytic leukemia: a longitudinal study. Sao Paulo Med J 2006; 124: 316-320.

[11] Zuo X, Chen J, Zhou X, Li X and Mei G. Levels of selenium, zinc, copper, and antioxidant enzyme activity in patients with leukemia. Biol Trace Elem Res 2006; 114: 41.

[12] Radhakrishnan N, Dinand V, Rao S, Gupta P, Toteja G, Kalra M, Yadav SP and Sachdeva A. Antioxidant levels at diagnosis in childhood acute lymphoblastic leukemia. Indian J Pediatr 2013; 80: 292-296.

[13] Carpentieri U, Myers J, Thorpe L, Daeschner CW and Haggard ME. Copper, zinc, and iron in normal and leukemic lymphocytes from children. Cancer Res 1986; 46: 981-984.
[14] Beguin Y, Brasseur F, Weber G, Bury J, Delbrouck JM, Roelandts I, Robaye G and Fillet G. Observations of serum trace elements in chronic lymphocytic leukemia. Cancer 1987; 60: 1842-1846.
[15] Al-Gayyar MM, Eissa LA, Rabie AM and El-Gayar AM. Measurements of oxidative stress status and antioxidant activity in chronic leukaemia patients. J Pharm Pharmacol 2007; 59: 409-417.
[16] Mazor D, Abucoider A, Meyerstein N and Kapelushnik J. Antioxidant status in pediatric acute lymphocytic leukemia (ALL) and solid tumors: the impact of oxidative stress. Pediatr Blood Cancer 2008; 51: 613-615.
[17] Kennedy DD, Ladas EJ, Rheingold SR, Blumberg J and Kelly KM. Antioxidant status decreases in children with acute lymphoblastic leukemia during the first six months of chemotherapy treatment. Pediatr Blood Cancer 2005; 44: 378-385.
[18] Er TK, Tsai SM, Wu SH, Chiang W, Lin HC, Lin SF, Wu SH, Tsai LY and Liu TZ. Antioxidant status and superoxide anion radical generation in acute myeloid leukemia. Clin Biochem 2007; 40: 1015-1019.
[19] Neyestani TR, Fereydouni Z, Hejazi S, Salehi-Nasab F, Nateghifard F, Maddah M and Karandish M. Vitamin C status in Iranian children with acute lymphoblastic leukemia: evidence for increased utilization. J Pediatr Gastroenterol Nutr 2007; 45: 141-144.
[20] Allin KH, Bojesen SE and Nordestgaard BG. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. J Clin Oncol 2009; 27: 2217-2224.
[21] Dayer D, Asadi ZT, Samie M, Reisiyan N, Kalantarian G and Vakhshiteh F. Evaluation of serum copper levels in patients with leukemia and lymphoma. DAMA International 2015; 4: 266-270.
[22] Halton JM, Atkinson SA and Barr RD. Growth and body composition in response to chemotherapy in children with acute lymphoblastic leukemia. Int J Cancer Suppl 1998; 11: 81-84.
[23] Marinovic D, Dorgeret S, Lescoeur B, Alberti C, Noel M, Czernichow P, Sebag G, Vilmer E and Léger J. Improvement in bone mineral density and body composition in survivors of childhood acute lymphoblastic leukemia: a 1-year prospective study. Pediatrics 2005; 116: e102-e108.
[24] Garmey EG, Liu Q, Sklar CA, Meacham LR, Mertens AC, Stovall MA, Yasui Y, Robison LL and Oeffinger KC. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the childhood cancer survivor study. J Clin Oncol 2008; 26: 4639.
[25] Fuemmeler BF, Pendzich MK, Clark K, Lovelady C, Rosoff P, Blatt J and Demark-Wahnefried W. Diet, physical activity, and body composition changes during the first year of treatment for childhood acute leukemia and lymphoma. J Pediatr Hematol Oncol 2013; 35: 437.