Evaluation of Serum Copper Levels in Patients with Leukemia and Lymphoma

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Abstract: Background: Copper is an important mineral involved in the regulation of body metabolism, which is required in different biological functions. Any significant change in its level in the body can be critical. The present study evaluated copper levels in the sera of patients with leukemia and lymphoma who had been referred to Ahvaz Shafa Hematology Oncology Hospital and compared the findings with those of a control group. **Methods:** In the current case-control study, 50 patients with leukemia and lymphomas and 50 healthy individuals were evaluated. Patients were classified into acute myeloid leukemia, acute lymphoblastic leukemia, and lymphoma groups. Blood samples were collected from patients and the control group, and copper levels in the sera were measured by the flame atomic absorption method. **Results:** The patients consisted of six (12%) males and 44 (88%) females, and healthy subjects consisted of 11 (22%) males and 39 (78%) females. The mean age of patients in the patient group and individuals in the control group was 22.4 and 22.6 years, respectively, ranging from 10–30 years. The patients group included patients with acute lymphoblastic leukemia (24 cases), acute myeloid leukemia (16 cases), and Hodgkin's and non-Hodgkin's lymphoma (10 cases). The average value for sera copper was 905 µg/l for patients, whereas the corresponding value for healthy controls was 801.1 µg/l. When patients were compared with controls, the serum copper was significantly higher ($p < 0.001$). **Conclusion:** Evidence of elevated levels of copper was observed in leukemia and lymphoma patients, which might suggest a role for this element in cancer as an independent risk factor for malignancy.

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Introduction

Leukemia and lymphoma originate in the bone marrow or lymphatic tissues and cause a high rate of mortality worldwide. In Iran, these diseases affect different age groups and cause high mortality as well as high expense of diagnosis and treatment for both families and country's health system, which is similar to other countries (1). Nowadays, the incidences of blood cancers, such as leukemia and lymphoma, have been increasing in human societies (2). These diseases are neoplasms of blood-forming and immune systems and are diagnosed with various clinical and pathological symptoms. From the etiology point of view, a wide range of genetic, chemical, physical, and other environmental factors have been revealed to be associated with these diseases (3, 4).

A combination of external and internal factors, including the presence of trace elements, play a role in the initiation and progression of neoplastic disease. Trace elements have been extensively studied over recent years. Among all minerals, zinc and copper are two important minerals in the regulation of body immunity (5). Zinc is an antioxidant element and a cofactor of more than 200 enzymes (6). Furthermore, copper is an essential antioxidant and coenzyme that is vital to the health of all living things (7). Changes in blood zinc and copper have been found in cancers, including breast, lung, and gastrointestinal as well as other types of malignant tumors (8).

Copper is a cofactor of over 30 enzymes and might play a role as a catalyst in the generation of active oxygen and the peroxidation reaction of membrane lipids (9-11). In the cytoplasm of eukaryotic cells, superoxide dismutase is an antioxidant enzyme with copper and zinc located at its active site (9, 12). In addition, copper plays a role in the chemical structure of catecholamine and ATP-producing enzymes (11, 12). Copper is a component of at least nine growth factors, particularly the endothelial growth factor, which results in tumor progression through angiogenesis upon an increase in sera copper levels (2, 9). Recent studies indicate the importance of sera copper to zinc ratios due to the high competition between these two elements to enter cells (13, 14). On the basis of previous reports, the increase in copper levels or the increase in copper to zinc ratio resulted in increase in lipid peroxidation, destruction of the antioxidant system, and generation of hydroxyl radicals via an increase in malondialdehyde. This in turn attacks DNA and causes mutations that lead to cancer (15, 16). The decrease in zinc level hinders the fair competition with entry of copper into tissues, which makes a favorable condition for copper to enter into tissues (13, 17). The biological function of trace elements, particularly changes in copper and zinc levels and their role in cancer, have been extensively investigated in recent years (18, 19). Therefore, the current study aimed to investigate the sera copper level in acute lymphoid leukemia, acute myeloid leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma patients compared with a normal group.

Methods

The case-control study was conducted from 2011–2012 and included 50 patients with leukemia (acute lymphoid leukemia and acute lymphoblastic leukemia) and lymphoma (Hodgkin's and non-Hodgkin's lymphoma) hospitalized in Ahvaz Hematology Oncology Shafa Hospital. For comparison of results, 50 healthy subjects were selected and subjected to full medical examination. The study was designed on the basis of principles of the Ethics Committee of the University of Medical Sciences in Ahvaz. All subjects received and signed written consent for voluntary participation in the study. The normal group health status was confirmed by clinical examinations (biochemical, hematological, microbial, serology, and hormone testing), and showed no symptoms of leukemia, lymphoma, or any other diseases. The patient group was diagnosed with leukemia or lymphoma confirmed by clinical testing, including morphological and cytological bone marrow sample assessments. Patients or control group members diagnosed with liver disease, alcoholism, chronic shortness of breath, skin disorders, infections, diarrhea, gastrointestinal, renal, cardiovascular, hypertension, diabetes, or those who received vitamin supplements and minerals, were excluded from the study.

Fifty samples of case and 50 samples of controls were investigated. Fasting blood samples were collected in acid-washed tubes, neuraminidase was added, and tubes were centrifuged at 3000 rpm for 10 min. Neuraminidase was added to minimize removal of ceruloplasmin by sialic acid residues from serum during clot formation. Sera was isolated from clots and stored at −20°C. Total concentration of copper in sera was measured by atomic absorption with flame system (Perkin Elmer 3030; Perkin Elmer,).Samples were diluted by 0.5% HNO3. The standard curve was obtained using different dilutions of standards. Copper levels were determined against a standard curve. All data were analyzed using the statistical Package for the Social Sciences (SPSS) software (version 17.0, Nie, Bent, and Hull, USA). The differences between copper levels in case and control groups were established using the t-test. The significance level was set as $p < 0.05$. The normal range was considered 500–1500 (µg/dl) for copper.

Results

The patients included 6 (12%) males and 44 (88%) females, and the healthy subjects included 11 (22%) males and 39 (78%) females. The mean age of patients and control group members were 22.4 and 22.6 years, respectively, ranging from 10–30 years. The patient groups included acute lymphoblastic leukemia (24 cases), acute myeloid leukemia (16 cases), and Hodgkin's and non-Hodgkin's lymphoma (10 cases, Table 1).

The average value for sera copper was 905 µg/l for patients and 801.1 µg/l for healthy subjects, indicating significant difference ($p < 0.001$), as illustrated in Table 2.

Discussion

With regard to the nutritional role of copper and zinc and their important roles in metabolism regulation (20) and their direct relation with cancers (8), any significant changes in the level of these elements could be harmful to the body (21). On the basis of different studies, the increase in copper or copper/zinc ratio leads to increased lipid peroxidation, destruction of the antioxidant system, and generation of hydroxyl radicals through increase in malondialdehyde, which attacks DNA and causes mutations that lead to cancer (15, 16). Meanwhile, copper is a component of the chemical structure of catecholamine and ATP-producing enzymes and is considered as one of the nine growth factors, particularly the endothelial growth factor. The endothelial growth factor causes tumor progression and angiogenesis upon increase in sera copper levels (2, 9). In the current study, copper levels in leukemia and lymphoma patients were higher than those in the normal group ($p < 0.001$). The results of the present study were in line with the results of Paulo *et al.* (2006) and Qunzhi *et al.*(2001) who indicated that patients with acute myeloid leukemia, acute lymphoblastic leukemia, and lymphoma had higher levels of sera copper than those in normal subjects (22, 23). Qunzhi *et al*. (2003) showed that the increase in copper level relates to histopathological changes, disease stage, and prognosis of patients with lymphoma (24). The results obtained by the flame atomic absorption method conducted by Zuo *et al.* (2006), and Qunzhi *et al*. (2003) indicated that sera copper levels were higher than those in the normal group (25, 24). Zarghami *et al*. (2009) and Geraki *et al*. (2002, 2004) showed that copper levels in leukemia patients showed a significant increase compared with normal subjects (19, 26, 27). The result of Carpentieri *et al*. (1986), in accordance with results of this study, indicated that there was no relation between the copper level and gender in either normal or patient groups (28). In addition, sera copper levels were not significantly associated with age, which is in line with results of Sgarbieri *et al.* (29).

Conclusion:

In this evaluation of sera copper levels in patients with leukemia and lymphoma, the existence of elevated levels of copper was observed in leukemia

and lymphoma patients, which might suggest a role of this element in cancer and might represent an independent risk factor for malignancy. Therefore, to increase the zinc/copper ratio, complementary zinc application is suggested for patients with leukemia and lymphoma.

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Table 1: Characteristics of patients and normal group

	n	F (%)	M (%)
ALL	24	12 (50)	12 (50)
AML	16	10 (62.5)	6 (37.5)
Lymphoma	10	3 (30)	7 (70)
Total	50	25 (25)	25 (25)
Control group	50	39 (78)	11 (22)

n: number
F: females
M: males

Table 2: Mean of Copper level in sera of patients and normal group

	n	M
ALL	24	919.5*
AML	16	945.2*
Lymphoma	10	937.9*
Total	50	905.0*
Control group	50	801.1

n: number;
M: mean copper concentration(µg/l)
*significant difference ($p<0.05$)

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