Original Article

Serum selenium levels in chronic lymphocytic leukemia

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Abstract

Background: Selenium is a trace mineral which has the role of multiple biologic functions. In free-living animals and humans, selenium is mostly in the form of two selenium-containing amino acids as selenocysteine and selenomethionine. The present study aimed to obtain more data on the relationship between serum selenium in chronic lymphocytic leukemia (CLL).

Materials and Methods: Serum selenium levels were measured in 51 patients with chronic lymphocytic leukemia (CLL) as patients group and in 40 non-hospitalized healthy individuals as control group.

Results: Selenium was recognized by atomic absorption spectrometer. Decreased mean serum selenium concentrations were observed in the group with chronic lymphocytic leukemia as compared to normal ones ($P = 0.005$). Serum selenium concentrations were examined in stages 0 and I. They observed a significant difference between the mean serum concentrations of selenium in stage 0, I and II and that of stage IV and V patients with CLL ($P = 0.01$). The groups were compared and significant differences were observed i.e., low serum selenium levels in the stage III and IV CLL ($P = 0.001$). The second selenium test was designed in 21 out of 48 patients within 10 weeks from the beginning of chemotherapy. Serum selenium concentration was tested again in 21 patients, and significant differences have been observed between the time before the treatment and after it ($P = 0.02$).

Conclusions: Our results show that in patients with CLL the mean serum selenium levels are lower than that of normal.

Key Words: Chronic lymphocytic, leukemia, serum selenium

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INTRODUCTION

Selenium is a trace mineral with multiple biologic functions.[1] In free-living animals and humans, selenium is mostly in the form of two selenium-containing amino acids as selenocysteine and seleno-methionine. More than 30 selenoproteins have been identified, of where of the best known are four forms of glutathione peroxidase which are important in antioxidant defense.[2] Selenium can be found in relatively high amounts in several tissues with hematopoietic and potential immune function, including liver, spleen, bone marrow and lymph nodes. Impaired cell-mediated immunity has been demonstrated when tissues storing selenium are depleted).[3]

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Epidemiologic studies are supported a possible relationship between selenium and cancer mortality.[4] Therefore, a number of studies have investigated the role of selenium supplementation in preventing the cancer.

Much scientific attention is currently drawn on the possible role of selenium as an antineoplastic drug and the hypothetical involvement of the trace element in the etiology of human cancer. There is much of evidence supporting the effects pharmacological doses of selenium have on cell proliferation and viability, suggesting possible use of selenium compounds as antineoplastic drugs.[5] This seems to be strictly related to the carcinostatic and cytotoxic activity of this compound.[6] Neoplasms of the lymphoid system account for one of the most frequently examined site-specific cancers that above mentioned control studies with cross-sectional design for analyzing possible relationship between serum concentrations of selenium and cancer.[7]

Selenium, an essential trace element involved in defense against oxidative stress, may prevent cancer and cardiovascular disease.[8]

Certain epidemiological, clinical and experimental investigations suggest that selenium protects against malignant tumors.[8,9]

Selenium levels were significantly lower in patients with carcinoma than in healthy controls.[3] On the contrary, for neoplasias of the reticuloendothelial system, levels lower than normal have been found.[3]

In the current study the association between serum selenium levels in chronic lymphocytic leukemia (CLL) was evaluated. According to the WHO classification, B-cell chronic lymphocytic leukemia is considered to be identical (i.e., one disease at different stages) to the mature (peripheral) B-cell neoplasm small lymphocytic lymphoma.[1-3] It is characterized by a progressive accumulation of functionally incompetent lymphocytes, which are monoclonal in origin. The present study attempted to obtain more data on the relationship between serum selenium in CLL.

MATERIALS AND METHODS

The CLL patients were staged through Rai classification system-The Rai system is a five stage classification based on an analysis of the manner the body is affected by the abnormal lymphocytes (1) and higher numbers indicate a more advanced stage of disease:

Stage 0: Increased numbers of abnormal lymphocytes are found in the blood or bone marrow; lymph nodes/organs are not swollen; and production of red cells and platelets are normal

Stage I: Increased abnormal lymphocytes and enlarged lymph nodes

Stage II: Increased abnormal lymphocytes with enlarged liver or spleen, with or without enlarged lymph nodes

Stage III: Increased abnormal lymphocytes with anemia (low red blood cell count), with or without an enlarged spleen, liver, or lymph nodes

Stage IV: Increased abnormal lymphocytes with a low platelet count, with or without anemia, enlarged liver, spleen, or lymph nodes.

A consecutive series of 51 patients who were newly diagnosed as chronic lymphocytic leukemia were enrolled in the study. These patients were recruited from Hematology and Oncologic Service of Sayed Al Shohada hospital in Isfahan city, none of the patients had been previously treated.

Venous blood was drawn in the morning after overnight fasting. Samples were immediately centrifuged for 10 min, and two serum aliquots of 1.5 ml from each patient were stored in plastic tubes at -12°C until analysis. Serum selenium assay and atomic absorption spectrometry technique were employed to determine selenium concentrations in serum samples.

Most of 51 patients with CLL were in stage 0, I, II, III and IV according to Rai classification system. None of the patients were treated before the serum selenium test. Out of 51 patients which 21 had a repeated serum selenium test within 10 weeks from the beginning of chemotherapy.

Forty normal subjects in both genders aged from 50 to 71 years coming from the same region underwent the same test as a control group [Table 1].

The statistical analysis was performed by Student's *t*-test by MedCalc version 9.3. (Independent Sample

Table 1: Healthy control group

Mean age (range)	No. of healthy control group	Gender
65 year (46-76)	23	Male
63 year (50-77)	17	Female
64 year (46-76)	40	Total patients group

T-test). Results are reported as mean ± standard error (SE).

RESULTS

Patient characteristics

Fifty one patients with CLL were into the study with median age of 64 years (range; 46-76 year). Twenty seven of those were male and 21 female.

Control group consist of 40 normal subjects with the same location living of the patients (23 male and 17 female) aged 50 to 71 years.

In this study, 51 patients with newly diagnosed CLL were found to have lower serum selenium levels than control subjects, (P = Selenium levels in patients with early disease stages (stage 0) were not significantly different from the values observed in controls (92.42 vs. 99.58 respectively).

Serum selenium levels in the whole patient group were significantly different from the values observed in controls ($P = 0.005$).

The results obtained from 5 groups of patients and for controls are reported in Table 1. There was observed a significant difference between the mean serum concentrations of selenium in stage 0, I and II and stage IV and V patients with CLL ($P = 0.01$). However, by comparing the groups, significant differences were found i.e., low serum selenium levels in stages III and IV CLL ($P < 0.001$). It should be pointed out that 22 patients in stages 0, I and II had the highest selenium levels. By comparing these groups (stage 0 and I) with control group no significant difference was found. Levels of selenium in stages 0 and I were not significantly different from the values observed in control subjects, whereas selenium concentrations in stage IV disease were significantly lower than controls ($P < 0.001$). After polychemotherapy (21 cases), serum selenium concentration was tested again, and significant differences have been observed before and after the treatment ($P = 0.02$).

Serum selenium concentrations according to Rai classification system stages in patients with CLL are shown in Table 2. These concentrations were inversely associated with stage, and significant differences were observed between patients in stages III and IV and stages 0, I and II CLL.

Table 2: Serum selenium levels (μg/L) in patients and controls

Stage of CLL	Selenium level μg/100 ml	F/M	Mean (age)	NO
0	94.85 ug/L	1/2	62 year	3
I	92.42 ug/L	2/3	68 year	5
II	84.64 ug/L	5/9	62 year	14
III	71.12 ug/L	4/9	66 year	13
IV	68.63 ug/L	5/11	64 year	16
Normal group	99.58 ug/L	13/27	64 year	40

DISCUSSION

The aim of the present study was relationship between serum selenium in CLL.

The results show that in patients with CLL the mean serum selenium levels are lower than normal.

There is a correlation between the selenium level and the clinical stage, none of our patients had been treated at the time of the first selenium test. This might reflect a selective selenium sequestration by CLL cells or global reduction of the selenium pool in this disease.

The fact that selenium is an integral part of glutathione peroxidase is an outstanding discovery which should be outlined in this regard.[3] The activity of this enzyme is partially related to serum selenium concentration in men. In 1973, reported that in CLL the erythrocytic glutathione peroxidase tends to be lower than in normal.[3] This suggests a relationship between selenium and glutathione peroxidase in this disease.[10]

The decreasing concentrations of selenium with disease progression might be due to disease-mediated dietary changes, which are more pronounced in patients with advanced disease. To the best of our knowledge, this hypothesis, however, was not tested in the present study or in previous investigations.

A second hypothesis to explain the decreasing levels of selenium in untreated cancer patients with very advanced disease arises from the observation that selenium compounds tend to concentrate in neoplastic tissues in a variety of human and animal tumors.[11-14] This phenomenon, which has been specifically examined in patients with Hodgkin's disease and Non-Hodgkin's lymphoma and in animal models of lymphoma,[15,16] represents the basis for the clinical use of labeled selenium compounds in tumor scintigraphy. Enhanced uptake of selenium by the neoplastic tissue might be responsible for depleting the trace element content of the blood and other tissues, thereby lowering serum selenium concentrations. It has also been noted in *in vivo* and *in vitro* animal studies preferential uptake of labeled selenium compounds decreases following tumor irradiation[17] and this fact might explain the lack of association between serum levels of selenium and the stage of the lymphoid malignancy when treated patients were examined.

In agreement with observations in patients with cancer and other diseases [18-20] but unlike what was found in a group of patients with reticuloendothelial tumors.[21] A direct association between albumin and serum selenium levels might be explained by nutritional factors or by the fact that albumin represents a selenium-containing protein,[22] it seems appropriate to examine the possible utility of determining selenium status in the clinical evaluation of patients with lymphoid malignancies.

More extensive studies, however, are needed to evaluate this possibility. Moreover, selenium status markers at clinical onset of a CLL might represent a prognostic factor of the disease, as recently suggested in epidermotropic cutaneous T-cell lymphoma.

Regarding the close relationship with tumor burden and the rapid modifications induced by chemotherapy, a mechanism of selenium sequestration by tumor cells is possible. There are some evidence reported, which indicate that certain tumors can accumulate selenium.[11,12]

Moreover, the cancer enhancing properties of selenium observed in some animal studies have been selectively associated with specific chemical forms of the trace element, such as hexavalent [23] or tetravalent inorganic selenium, suggesting that analysis of exposure rather than evaluation of selenium status might be useful for detecting an association between selenium and human cancer. The results of the present study suggest that a low selenium status represents a risk factor for CLL, since the serum concentrations of selenium in patients with localized disease were not lower than those observed in controls. We believe that unless all these aspects of selenium metabolism in CLL patients are clearly sorted out, incorporation of selenium supplementation into an overall therapeutic strategy would not be warranted. The findings of the study are in accordance with observations made in CLL, it shows a tendency for serum selenium levels be decreased with progression of the disease, and that selenium levels in patients with early disease stages were not significantly different from the values observed in controls.

It has been suggested that chemotherapy might increase the release of selenium into the blood from the neoplastic tissue, which has higher selenium content than the time before chemotherapy.

In conclusion, the results of the present study suggest that the serum concentration of selenium in newly diagnosed CLL is inversely associated with the clinical stage of the disease, but this relationship needs to be confirmed in future studies.

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